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(54) PYRIMIDINE ACYCLONUCLEOSIDE DERIVATIVES

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DERIVES ACYCLONUCLEOSIDES PYRIMIDIQUES

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- **Antiviral Chemistry and Chemotherapy, 1992, 3(5), 263-266, Gougadon et al. "1-(Ethoxymethyl)-6-(phenylselenenyl)pyrimidines with activity against immunodeficiency virus types 1 and 2"**

Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

EP 0 748 316 B1

Description

FIELD OF THE INVENTION

[0001] The present invention relates to novel pyrimidine acyclonucleoside derivatives, antiviral agents containing the derivative as the active ingredients and processes of preparation therefore.

BACKGROUND OF THE INVENTION

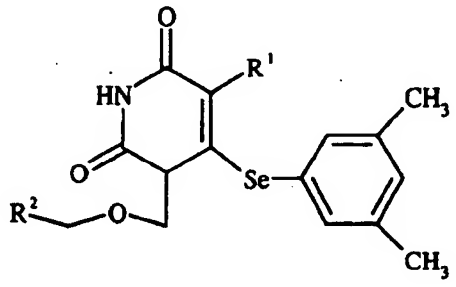
[0002] AIDS (Acquired immunodeficiency syndrome), caused by human immunodeficiency virus (HIV), is one of the world's most serious health problems.

[0003] 3'-Deoxy-3'-azidothymidine (AZT), which is available in the clinic, has been proven to improve the clinical and immunological status of patients with AIDS and AIDS-related complex. However, serious side effects such as anemia and leukopenia strongly limit its clinical usefulness. Although 2',3'-dideoxyinosine (DDI) and 2',3'-dideoxycytidine (DDC) have more recently been approved for the patients who do not tolerate AZT, they are also suffering from side effects such as peripheral neuropathy and pancreatitis. Therfore, there is an urgent need to develop a substance possessing higher antiviral activity and lower toxicity to the host cells. Various pyrimidine acyclonucleoside derivatives having (substituted) phenylthio group or (substituted) benzyl group at the 6-position of the pyrimidine ring have been disclosed and found to have effective antiviral activity against retrovirus (WO 89/09213, EP 420,763 A2, EP 449,726 A1). A few 6-phenylselenenyl substituted pyrimidine acyclonucleoside derivatives (*J. Med. Chem.* **1991**, *34*, 3305-3309, *Antiviral Chem. & Chemother.* **1992**, *3(5)*, 263-266 and *J. Heterocyclic Chem.* **1994**, *31*, 177-185) have been synthesized, however, the antiviral activity against retrovirus is only marginal. The present inventors have synthesized novel pyrimidine acyclonucleoside derivatives having ethyl group or isopropyl group at the 5-position and having (substituted) phenylselenenyl group at the 6-position of the pyrimidine ring, and found that most of these pyrimidine acyclonucleoside derivatives possessed excellent anti-retroviral activity to satisfy the above demand (KR Application No. 94-3794, 94-18324 and 94-18325). The present invention has been accomplishied based on this finding.

SUMMARY OF THE INVENTION

[0004] A primary objective of the present invention is to provide novel pyrimidine acyclonucleoside derivatives having improved antiviral activity.

[0005] This problem is solved by a pyrimidine acyclonucleoside derivative represented by the following general formula (I):



(I)

wherein
R^1 is ethyl group or isopropyl group, and
R^2 is methyl group or phenyl group,
or a pharmaceutically acceptable salt thereof.

[0006] The pyrimidine acyclonucleoside derivative according to the present invention is
1-(ethoxymethyl)-5-ethyl-6-[(3,5-dimethylphenyl)-selenenyl]-uracil,. or
1-(benzyloxymethyl)-5-ethyl-6-[(3,5-dimethylphenyl)-selenenyl]-uracil, or
1-(ethoxymethyl)-5-isopropyl-6-[(3,5-dimethylphenyl)-selenenyl]-uracil, or
1-(benzyloxymethyl)-5-isopropyl-6-[(3,5-dimethylphenyl)-selenenyl)-uracil, or
a pharmaceutically acceptable salt thereof.

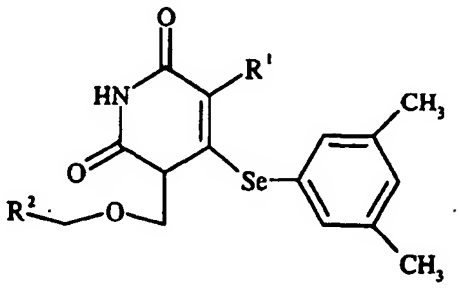
[0007] According to another aspect of the present invention there is provided an antiviral agent containing pyrimidine

acyclonucleoside derivative of general formula (I) or pharmaceutically acceptable salt thereof as active ingredient.

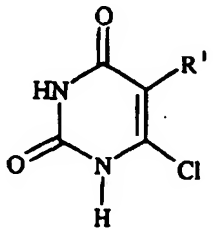
[0008] According to another aspect of the present invention there is provided an antiviral agent comprising as an active ingredient a pyrimidine acyclonucleoside derivative or a pharmaceutically acceptable salt thereof according to the above formula (I).

[0009] According to another aspect of the present invention there is provided a pharmaceutical composition comprising a pyrimidine acyclonucleoside derivative of the above formula (I) or a pharmaceutically acceptable salt thereof in association with a pharmaceutical vehicle.

[0010] According to another aspect of the present invention there is provided a method for preparing a pyrimidine acyclonucleoside derivative represented by the following general formula (I) comprising the steps of reacting an uracil of the general formula (II) with N,O-bis-(trimethylsilyl)-acetamide followed by tetrabutylammonium iodide and a chloromethyl ether of the general formula (III), and reacting a compound of the following general formula (IV) with an aryl selenol in the presence of base, wherein R_1 represents ethyl group or isopropyl group and R_2 represents methyl group or phenyl group.

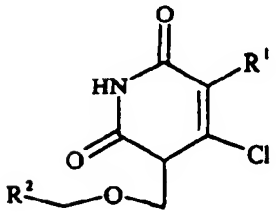


(I)



(II)

(III)



(IV)

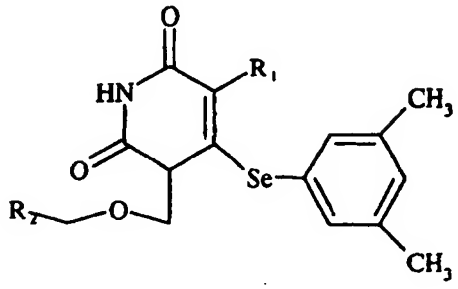
DETAILED DESCRIPTION OF THE INVENTION

[0011] The pyrimidine acyclonucleoside derivatives according to the invention are represented by the general formula (I). In the general formula (I), the group of R^1 represents ethyl group or isopropyl group. The group of R^2 represents

methyl or phenyl group.

[0012] Examples of the preferred compounds of the present invention are listed in Table 1 below.

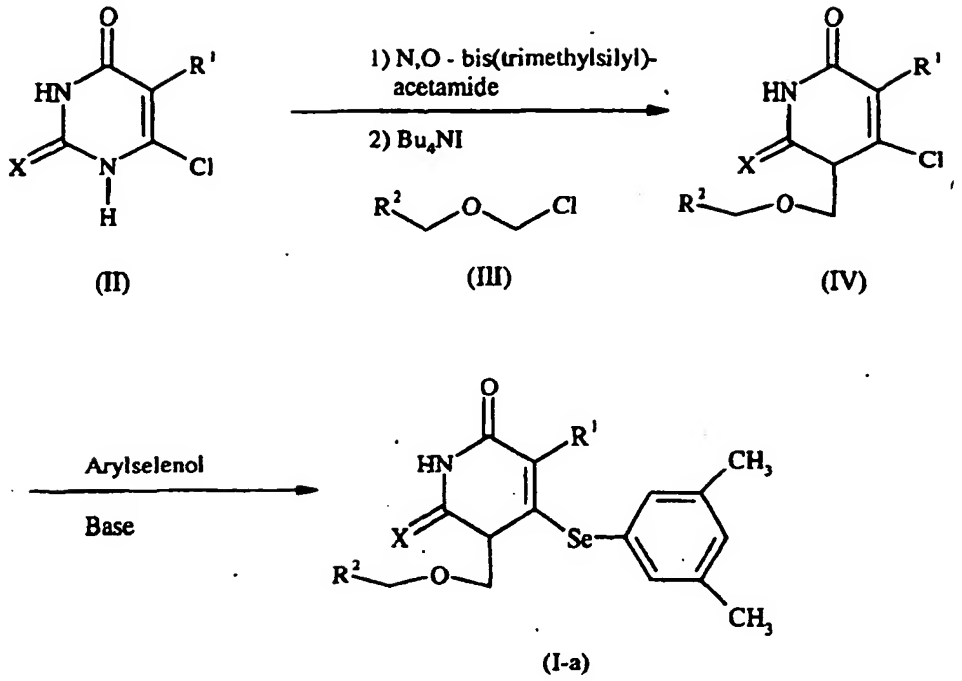
Table 1



Compound No.	R^1	R^2
1	$-C_2H_5$	$-CH_3$
2	$-C_2H_5$	
3	$-CH(CH_3)_2$	$-CH_3$
4	$-CH(CH_3)_2$	

[0013] The compounds represented by the following general formula(I-a) may be prepared in accordance with the following reaction Scheme (1), (2) or (3):

Scheme (1)

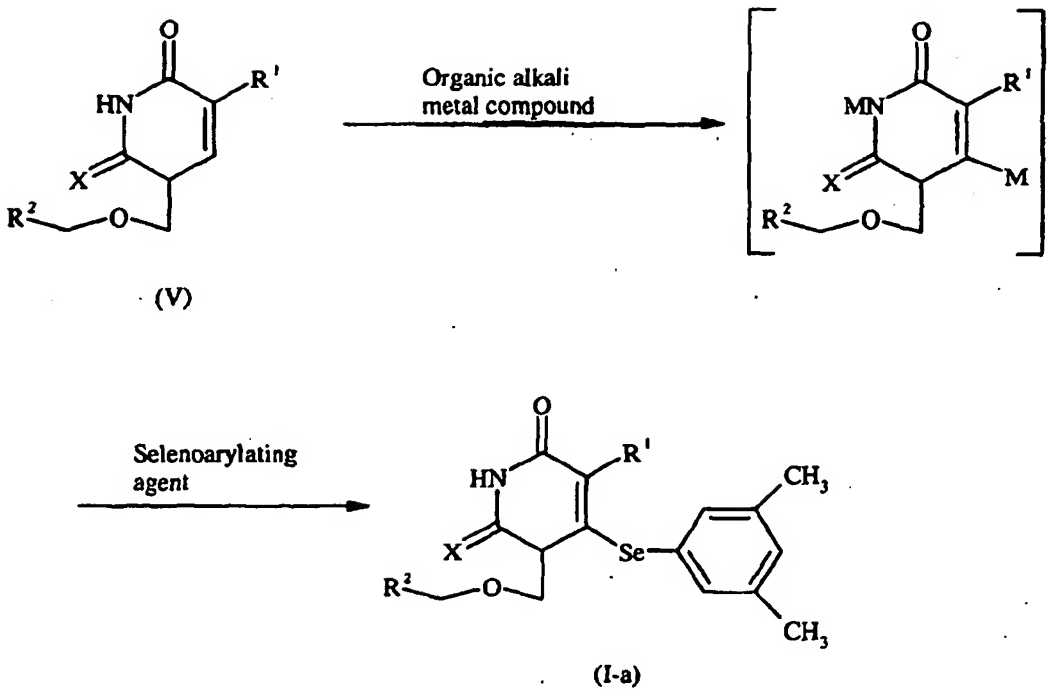


(II) (III) (IV)

(I-a)

wherein R^1 and R^2 represent the same as defined in the general formula (I). X represents oxygen or sulfur atom. When X represents sulfur atom, compound I-a can be converted according to reaction scheme (4) herebelow to obtain the compound according to the invention having X = oxygen.. As illustrated above, 1 mole of compound of the general formula (II) is treated with 2 to 4 moles of *N,O*-bis(trimethylsilyl)acetamide in dichloromethane at 0°C to 50°C for 0.5 to 5 hours. Then, about 0.01 to 0.05 moles of tetrabutylammonium iodide and 1 to 4 moles of chloromethyl ether represented by the general formula (III) are added to allow the reaction at a temperature of -50°C to 50°C for 0.5 to 5 hours to provide the compound represented by the general formula (IV). The compound of the general formula (IV) is reacted with 1 to 2 moles of aryl selenol and alcoholic solution (methanol or ethanol) of sodium hydroxide at 15°C to 30°C for 5 minutes to 5 hours to provide the compound represented by the general formula (I-a). The resulting compound of the present invention represented by the general formula (I-a) can be separated and purified by appropriate conventional methods such as column chromatography and recrystallization.

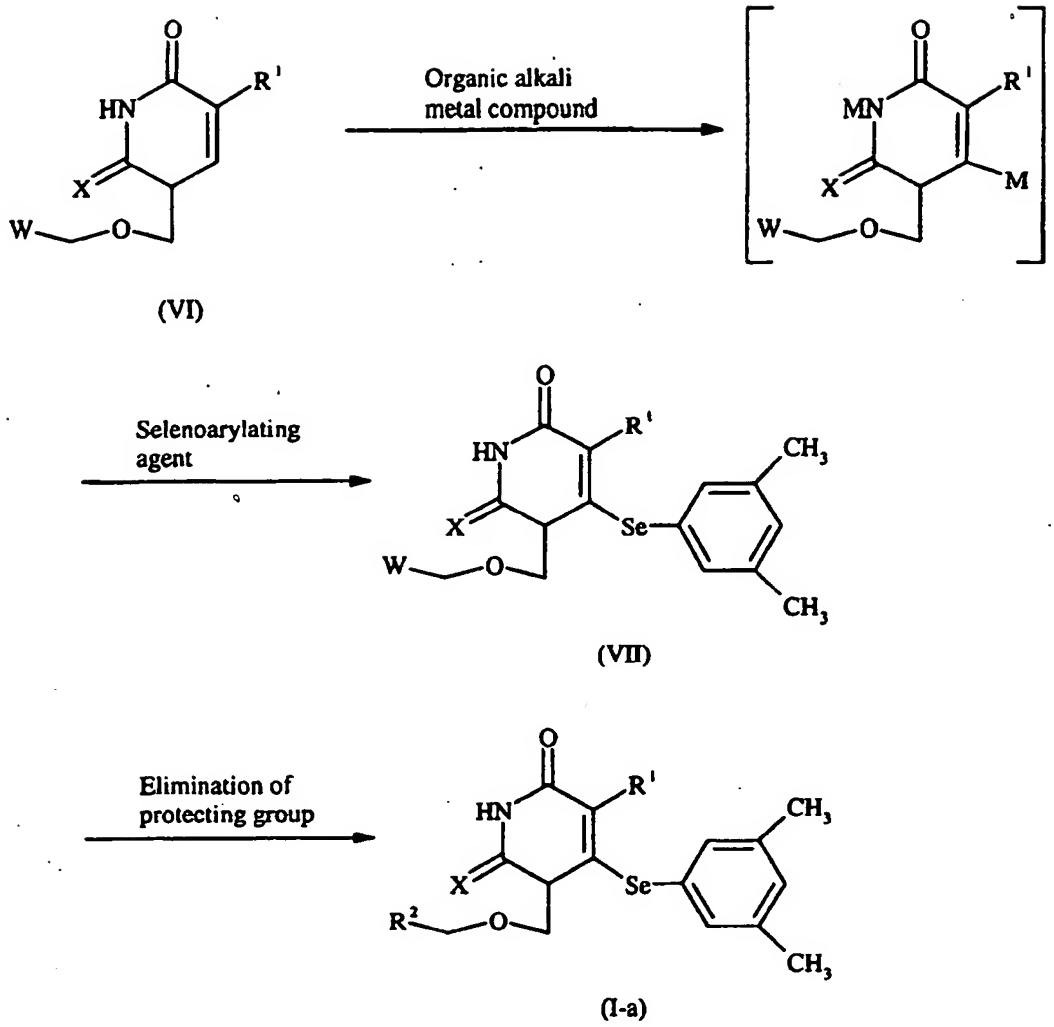
Scheme (2)



(V)

(I-a)

Scheme (3)



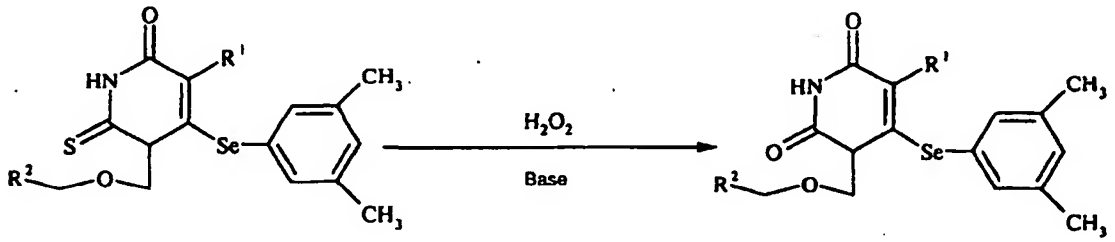
wherein R^1, R^2, and X represent the same as defined above. W represents the group of R^2 having a protected hydroxy group, and M represents an alkali metal. Any conventional protective group which does not undergo elimination under alkaline condition may be used for the group of W, i.e., the protection of the hydroxyl group of R^2. Examples of such a protective group are an aralkyl group such as benzyl, trityl, monomethoxytrityl, dimethoxytrityl, trimethoxytrityl, and the like; a silyl group such as trimethylsilyl, triethylsilyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl, and the like; and a substitued alkyl group such as tetrahydropyranyl, methoxymethyl, and the like. Among these protective groups, silyl groups may be most preferable. The compound of the general formula (V) or (VI) is firstly treated with an organic alkali metal compound in an ether solvent such as tetrahydrofuran and diethyl ether at a temperature of from -80 to 0°C for 0.1 to 10 hours. Examples of the organic alkali metal compounds are lithium bis(trimethylsilyl)amide, potassium bis (trimethylsilyl)amide, sodium bis(trimethylsilyl)amide, lithium diisopropylamide (LDA) and lithium 2,2,6,6-tetramethyl-piperidide (LTMP). Of these, lithium diisopropylamide (LDA) and lithium bis(trimethylsilyl)amide may be most preferable.

[0014] The organic alkali metal compound is generally used in an amount of 2 to 5 moles per mole of the compound represented by the general formula (V) or (VI). Then, about 1 to 5 moles of a selenoarylating agent is added to 1 mole of the compound represented by the general formula (V) or (VI) to allow the reaction at a temperature of from -80 to 30°C for 0.1 to 24 hours to provide the compound represented by the general formula (I-a) or (VII). The selenoarylating agents should be those having a 3,5-dimethylphenyl-selenenyl group. Examples of the selenoarylating agents are various diaryl diselenides. The compound represented by the general formula (V) or (VI) as a starting material can be prepared by a conventional method. Then, the protective group may be eliminated from the thus obtained compound

represented by the general formula (VII). The elimination of the protective group can be carried out by a conventional method according to the kind of the protective group, for example, by hydrolysis, treatment with ammonium fluoride or catalytic reduction. The resulting compound of the present invention represented by the general formula (I-a) can be separated and purified by an appropriate conventional method such as column chromatography and recrystallization.

[0015] The compounds where X is a sulfur atom, which are obtained in the reaction Scheme (1), (2) or (3), may be converted into the corresponding compounds where X is an oxygen atom in accordance with the reaction Scheme (4) below:

Scheme (4)

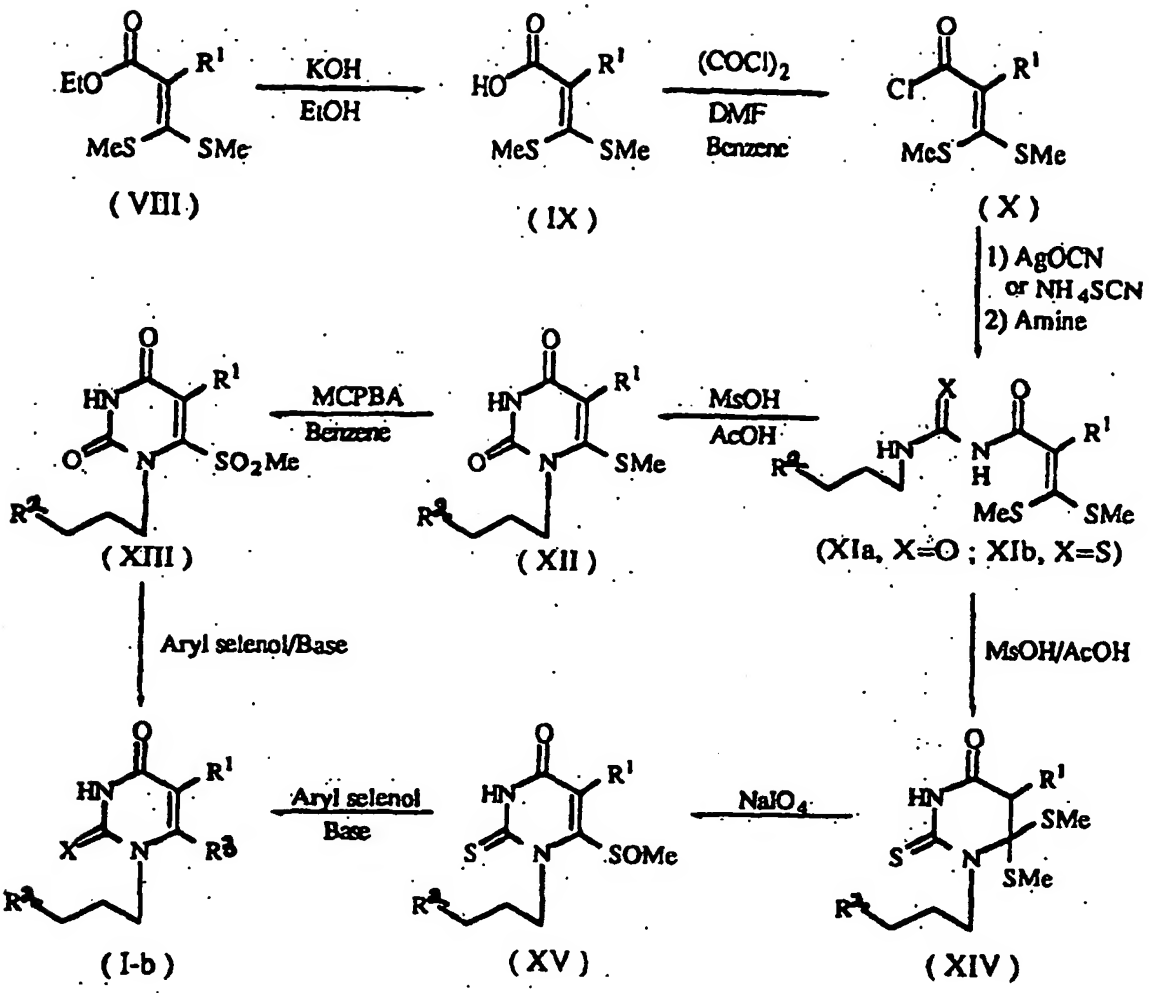


wherein R^1 and R^2 represent the same as defined above.

[0016] The reaction may be carried out in an aqueous alkaline medium such as sodium hydroxide solution and potassium hydroxide solution by treating with 30-35% aqueous hydrogen peroxide solution in an amount of 1 to 20 times of the starting compound at a suitable temperature from 0 to 50°C for 0.1 to 24 hours.

[0017] Besides the compounds represented by the following general formula(I-b) may be prepared in accordance with the following reaction Scheme (5):

Scheme (5)



wherein R^1, R^2 and X represent the same as defined in the general formula (I), and R^3 represents 3,5-dimethylphenyl-selenenyl group. As illustrated above, first, a readily prepared compound of general formula (VIII) in accordance with the method described in *J. Chem. Soc., Chem. Commun.*, 684 (1989) or *Bull. Inst. Chem. Res.*, Kyoto Univ., 68, 199 (1990), is treated with aqueous potassium hydroxide solution in ethanol at reflux temperature for 3 to 72 hours to obtain an acid of general formula (IX). The compound of general formula (IX) thus obtained is reacted with oxalyl chloride in benzene in the presence of a catalytic amount of *N,N*-dimethylformamide at 0 to 80°C for 1 to 24 hours to give a acid chloride of general formula (X). The compound of general formula (X) is treated with silver cyanate or ammonium thiocyanate in benzene at reflux temperature for 0.5 to 5 hours followed by an appropriate amine at -78 to 40°C for 0.5 to 5 hours to give an acryloylurea of general formula (XIa) or acryloylthiourea of general formula (XIb), respectively. The compound of general formula (XIa) is cyclized with 0.1 to 0.3 moles of methanesulfonic acid (MsOH) in acetic acid (AcOH) at 60 to 100°C for 1 to 24 hours to afford a 6-methylthiouracil of general formula (XII). Oxidation of the compound of general formula (XI) with m-chloroperbenzoic acid (MCPBA) in benzene at reflux temperature for 1 to 24 hours gave a 6-methylsulfonyluracil of general formula (XIII). The compound of general formula (XIb) is cyclized with 1 to 3 moles of methanesulfonic acid in acetic acid at 15 to 30°C for 5 minutes to 5 hours to afford a compound of general formula (XIV). The compound of general formula (XIV) is treated with 3 to 10 moles of aqueous solution of sodium periodate in methanol at reflux temperature for 1 to 5 hours to give a 6-methylsulfinyl-2-thiouracil of general formula (XV). Finally, the compound of general formula (XIII) or general formula (XV) is reacted with 1 to 2 moles of aryl selenol and methanolic solution of sodium hydroxide at 15 to 30°C for 5 minutes to 5 hours to provide the compound represented by the general formula (I-b). The aryl selenol should be those having a group of R^3 defined. above. The resulting compound of the present invention represented by the general formula (I-b) can be separated and purified

by an appropriate conventional method such as column chromatography and recrystallization.

[0018] The pyrimidine acyclonucleoside derivative of the present invention may be made into a pharmaceutically acceptable salt by conventional methods. Examples of such salts may include alkali metal salts such as sodium salt, potassium salt and the like; alkaline earth metal salts such as magnesium salt and the like; and ammonium salts such as ammonium salt, methylammonium salt, dimethylammonium salt, trimethylammonium salt, tetramethylammonium salt and the like.

[0019] The pyrimidine acyclonucleoside derivatives of the present invention can be administered to a patient through any of the usual routes such as oral, parenteral and local administrations for the purpose of preventing infection of retroviruses and the like or treating infectious diseases caused by these viruses. The effective dose of the pyrimidine acyclonucleoside derivative may vary with the age, physical condition, body weight and the like of each patient. In general, the appropriate administration dose of the derivative of the present invention may be in the range of from 1 to 100 mg/kg (body weight)/day, preferably 5 to 50 mg/kg (body weight)/day. Administration of the derivative of the present invention may be made once a day or a few times a day within the above range of dose. The compounds of the present invention are generally prepared in a pharmaceutical composition with suitable carrier, excipient and other additives. The carriers may be in either a solid or a liquid form. Examples of solid carriers may include lactose, kaolin, sucrose, crystalline cellulose, corn starch, talc, pectin, agar, stearic acid, magnesium stearate, lecithin, sodium chloride and the like. Examples of liquid carriers may include glycerin, peanut oil, polyvinyl pyrrolidone, olive oil, ethanol, benzyl alcohol, propylene glycol, water and the like. The antiviral agent of the present invention can be made into various forms.

[0020] For example, when solid carriers are used, the antiviral agent can be made into tablet, capsule, powder, granule, suppository, troche and the like. When liquid carriers are used, it can be made into emulsion, syrup, soft gelatin capsule, gel, paste, injection solution and the like. The novel pyrimidine acyclonucleoside derivatives according to the present invention have an effective antiviral activity against viruses such as retrovirus and have a relatively low toxicity against the host cell, therfore, the derivatives of the present invention are extremely useful as an active ingredient of antiviral agent.

EXAMPLES

[0021] The present invention is further illustrated in the following example, which should not be taken to limit the scope of the invention.

Preparative Example 1:

Preparation of 6-chloro-1-(ethoxymethyl)-5-isopropyluracil (a compound of the general formula (IV) wherein R^1 = CH $(CH_3)_2$, R^2=CH_3 and X=O)

[0022] To a stirred suspension of 6-chloro-5-isopropyluracil (566 mg, 3.0 mmol) in anhydrous CH_2Cl_2 (9 mL) at room temperature under a nitrogen atmosphere was slowly added *N,O*-bis(trimethylsilyl)acetamide (1.41 g, 6.6 mmol, 1.72 mL) via a syringe and the mixture was stirrred for an additional 2 h at room temperature. To the resulting clear reaction mixture was added Bu_4NI (11 mg, 0.03 mmol) in one portion at room temperature and the mixture was cooled to 0 °C immediately. Chloromethyl ethyl ether (591 mg, 6.0 mmol, 0.58 mL) was slowly added to the reaction mixture at 0 °C and the mixture was stirred for 2 h in an ice bath. The reaction mixture was poured into saturated $NaHCO_3$ solution (25 mL) and ice (25 g), and was stirred for 30 min. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (20 mL). The combined CH_2Cl_2 solution was washed with brine (20 mL), dried over anhydrous $MgSO_4$ and evaporated to dryness to afford a yellow solid. The crude product was purified by flash column chromatography on silica gel with EtOAc-hexane (1:2) as eluent to afford the titled compound (658 mg, 89%). Crystallization from EtOAc-hexane gave an analytically pure product.

IR (KBr): 1714, 1643, 1453 cm^{-1}

^1H NMR ($CDCl_3$/TMS) : δ 1.24 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 1.30 (d, *J* = 6.9 Hz, 6 H, $CH(CH_3)_2$), 3.21 (septet, *J* = 6.9 Hz, 1 H, $CH(CH_3)_2$), 3.67 (q, *J* = 7.2 Hz, 2 H, OCH_2CH_3), 5.50 (s, 2 H, NCH_2O); 9.00 (br s, 1 H, NH)

^{13}C NMR($CDCl_3$): δ 15.04, 29.22, 65.41, 74.85, 118.61, 142.49, 150.22, 160.77

Preparative Example 2:

Preparation of 6-chloro-1-(ethoxymethyl)-5-ethyluracil (a compound of the general formula (IV) wherein R^1 = C_2H_5, R^2= CH_3 and X=O)

[0023] The titled compound was prepared in the same manner as described in Preparative Example 1 by using 6-chloro-5-ethyluracil in place of 6-chloro-5-isopropyluracil.

Yield: 93%
IR (KBr): 1722, 1667, 1455 cm^{-1}
^1H NMR ($CDCl_3$/TMS) : δ 1.10 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 1.23 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 2.56 (q, J = 7.4 Hz, 2 H, CH_2CH_3), 3.67 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 5.50 (s, 2 H, NCH_2O), 9.68 (br s, 1 H, NH)
^{13}C NMR($CDCl_3$): δ 12.20, 15.01, 20.08, 65.40, 74.75, 116.07, 143.09, 150.34, 161.50

Preparative Example 3:

Preparation of 1-[(benzyloxy)methyl]-6-chloro-5-isopropyluracil (a compound of the general formula (IV) wherein R^1 = $CH(CH_3)_2$, R^2= Ph and X=O)

[0024] To a stirred suspension of 6-chloro-5-isopropyluracil (566 mg, 3.0 mmol) in anhydrous CH_2Cl_2 (9 mL) at room temperature under a nitrogen atmosphere was slowly added *N,O*-bis(trimethylsilyl)acetamide (1.41 g, 6.6 mmol, 1.72 mL) via a syringe and the mixture was stirrred for an additional 2 h at room temperature. To the resulting clear reaction mixture at room temperature was added Bu_4NI (11 mg, 0.03 mmol) in one portion followed by benzyl chloromethyl ether (593 mg, 3.6 mmol, 0.53 mL) and the mixture was refluxed in an oil bath for 2 h. The reaction mixture was cooled to room temperature and was poured into saturated $NaHCO_3$ solution (25 mL) and ice (25 g). The mixture was stirred for 30 min, the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (20 mL). The combined CH_2Cl_2 solution was washed with brine (20 mL), dried over anhydrous $MgSO_4$ and evaporated to dryness to afford a yellow solid. The crude product was purified by flash column chromatography on silica gel with EtOAc-hexane (1:2) as eluent to afford the titled compound (865 mg, 94%). Crystallization from EtOAc-hexane gave an analytically pure product.
IR (KBr): 1705, 1678, 1439 cm^{-1}
^1H NMR ($CDCl_3$/TMS) : δ 1.27 (d, J = 6.9 Hz, 6 H, $CH(CH_3)_2$), 3.20 (septet, J = 6.9 Hz, 1 H, $CH(CH_3)_2$), 4.70 (s, 2 H, OCH_2Ph), 5.59 (s, 2 H, NCH_2O), 7.26-7.40 (m, 5 H, Ar H), 8.68 (br s, 1 H, NH)
^{13}C NMR($CDCl_3$) : δ 19.52, 29.16, 72.09, 74.89, 118.69, 137.21, 142.26, 150.11, 160.50

Preparative Example 4:

Preparation of 1-[(benzyloxy)methyl]-6-chloro-1-ethyluracil (a compound of the general formula (IV) wherein $R^1 = C_2H_5$, R^2= Ph and X=O)

[0025] The titled compound was prepared in the same manner as described in Preparative Example 3 by using 6-chloro-5-ethyluracil in place of 6-chloro-5-isopropyluracil.
Yield: 88%
IR (KBr): 1700, 1671, 1446 cm^{-1}
^1H NMR ($CDCl_3$/TMS) : δ 1.08 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 2.52 (q, J = 7.5 Hz, 2 H, CH_2CH_3), 4.70 (s, 2 H, OCH_2Ph), 5.58 (s, 2 H, NCH_2O), 7.26-7.34 (m, 5 H, Ar H), 9.50 (br s, 1 H, NH)
^{13}C NMR($CDCl_3$) : δ 12.19, 20.24, 72.02, 74.74, 76.58, 116.16, 127.58, 127.94, 128.40, 137.13, 142.88, 150.25, 161.27

Preparative Example 5 :

Preparation of 1-(ethoxymethyl)-5-ethyl-2-thiouracil (a compound of the general formula (V) wherein $R^1=C_2H_5$, $R^2=CH_3$ and X=S)

[0026] A strirred suspension of 5-ethyl-2-thiouracil (9.00 g, 57.6 mmol) and $(NH_4)_2SO_4$ (1.20 g) in 1,1,1,3,3,3-hexamethyldisilazane (170 mL) was heated at reflux for 16 h under a nitrogen atmosphere. Volatile materials were evaporated *in vacuo* with protection against moisture. The residual oil was dissolved in MeCN (300 mL), and to the solution were added chloromethyl ethyl ether (6.53 g, 69.1 mmol, 6.4 mL) and CsI (15.00 g, 57.6 mmol). The mixture was heated at reflux for 2 h under a nitrogen atmosphere and allowed to cool to room temperature. The reaction mixture was poured into H_2O (300 mL) and then it was extracted with EtOAc (3 X 300 mL). The organic phase was washed with saturated $NaHCO_3$ solution (300 mL), dried over anhydrous $MgSO_4$ and concentrated to dryness. The residue was purified by flash column chromatography on silica gel with $CHCl_3$ as eluent and then crystallized from 2-propanol to give 4.35 g (35%) of the target compound.
IR(KBr): 1680 cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 1.17 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 1.25 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 2.42 (dq, J = 0.9 Hz, J = 7.5 Hz, 2 H, CH_2CH_3), 3.69 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 5.61 (s, 2 H, NCH_2O), 7.26 (d, J = 0.9 Hz, 1 H, H-6), 9.62 (br s, 1 H, NH)

Preparative Example 6 :

Preparation of 1-(ethoxymethyl)-5-isopropyl-2-thiouracil (a compound of the general formula (V) wherein R^1=CH $(CH_3)_2$, R^2=CH_3 and X=S)

[0027] The titled compound was prepared in the same manner as described in Preparative Example 5 by using 5-isopropyl-2-thiouracil in place of 5-ethyl-2-thiouracil.
Yield : 27%
IR (KBr) : 1674 cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 1.19 (d, *J* = 6.9 Hz, 6 H, $CH(CH_3)_2$), 1.25 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 2.94 (septet, *J* = 6.9 Hz, 1 H, $CH(CH_3)_2$), 3.69 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 5.16 (s, 2 H, NCH_2O), 7.23 (s, 1 H, H-6), 9.49 (br s, 1 H, NH)

Preparative Example 7:

Preparation of 1-[(benzyloxy)methyl]-5-ethyl-2-thiouracil (a compound of the general formula (V) wherein R^1=C_2H_5, R^2=C_6H_5 and X=S)

[0028] The titled compound was prepared in the same manner as described in Preparative Example 5 by using benzyl chloromethyl ether in place of chloromethyl ethyl ether.
Yield : 29%
IR (KBr) : 3448, 1654 cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 1.13 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 2.37 (q, *J* = 7.5 Hz, 2 H, CH_2CH_3), 4.72 (s, 2 H, CH_2Ph), 5.71 (s, 2 H, NCH_2O), 7.20 (s, 1 H, H-6), 7.25-7.45 (m, 5 H, Ar H), 9.37 (br s, 1 H, NH)

Preparative Example 8 :

Preparation of 1-[(benzyloxy)methyl]-5-isopropyl-2-thiouracil (a compound of the general formula (V) wherein R^1=CH $(CH_3)_2$, R^2=C_6H_5 and X=S)

[0029] The titled compound was prepared in the same manner as described in Preparative Example 5 by using 5-isopropyl-2-thiouracil and benzyl chloromethyl ether in place of 5-ethyl-2-thiouracil and chloromethyl ethyl ether, respectively.
Yield : 27%
IR (KBr): 3446, 1678 cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 1.15 (d, *J* = 6.9 Hz, 6 H, $CH(CH_3)_2$), 2.90 (septet, *J* = 6.9 Hz, 1 H, $CH(CH_3)_2$), 4.72 (s, 2 H, CH_2Ph), 5.72 (s, 2 H, NCH_2O), 7.17 (s, 1 H, H-6), 7.36 (m, 5 H, Ar H), 9.45 (br s, 1 H, NH)

Preparative Example 9 :

Preparation of 1-(ethoxymethyl)-5-ethyluracil (a compound of the general formula (V) wherein R^1=C_2H_5, R^2=CH_3 and X=O)

[0030] A suspension of 5-ethyluracil (3.50 g, 25.0 mmol) and *N,O*-bis(trimethylsilyl)acetamide (11.19 g, 55.0 mmol, 13.6 mL) in CH_2Cl_2 (30 mL) was stirred at room temperature for 2 h under a nitrogen atmosphere. To the resulting solution, Bu_4NI (93 mg, 0.25 mmol) and chloromethyl ethyl ether (2.84 g, 30.0 mmol, 2.8 mL) were added. The mixture was heated at reflux for 2 h and allowed to cool to room temperature. The reaction mixture was poured into saturated $NaHCO_3$ solution (10 mL) and ice (5 mL), and stirred for an additional 30 min. The organic phase was washed with brine (15 mL), dried over anhydrous $MgSO_4$ and concentrated to dryness. The residue was crystallized from EtOH to give 4.39 g (89%) of the target compound.
IR (KBr) : 3218, 1694 cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 1.15 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 1.22 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 2.38 (q, *J* = 7.5 Hz, 2 H, CH_2CH_3), 3.61 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 5.16 (s, 2 H, NCH_2O), 7.10 (s, 1 H, H-6), 9.41 (br s, 1 H, NH)
^{13}C NMR ($CDCl_3$): δ 12.62, 14.89, 19.90, 64.99, 76.22, 117.36, 138.08, 151.20, 163.79

Preparative Example 10 :

Preparation of 1-(ethoxymethyl)-5-isopropyluracil (a compound of the general formula (V) wherein R^1=$CH(CH_3)_2$, R^2=CH_3 and X=O)

[0031] The titled compound was prepared in the same manner as described in Preparative Example 9 by using 5-isopropyluracil in place of 5-ethyluracil.
Yield : 90%
IR (KBr) : 3230, 1698 cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 1.17 (d, *J* = 6.9 Hz, 6 H, $CH(CH_3)_2$), 1.23 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 2.92 (septet, *J* = 6.9 Hz, 1 H, $CH(CH_3)_2$), 3.62 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 5.16 (s, 2 H, NCH_2O), 7.07 (s, 1 H, H-6), 9.35 (br s, 1 H, NH)
^{13}C NMR ($CDCl_3$): δ 14.90, 21.47, 25.72, 65.02, 76.31, 121.79, 137.19, 151.05, 163.39

Preparative Example 11 :

Preparation of 1-[(benzyloxy)methyl]-5-ethyluracil (a compound of the general formula (V) wherein R^1=C_2H_5, R^2=C_6H_5 and X=O)

[0032] The titled compound was prepared in the same manner as described in Preparative Example 9 by using benzyl chloromethyl ether in place of chloromethyl ethyl ether.
Yield: 83%
IR (KBr) : 3446, 1702, 1660 cm^{-1}
'H NMR ($CDCl_3$/TMS): δ 1.12 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 2.35 (q, *J* = 7.5 Hz, 2 H, CH_2CH_3), 4.63 (s, 2 H, CH_2Ph), 5.23 (s, 2 H, NCH_2O), 7.05 (s, 1 H, H-6), 7.30-7.40 (m, 5 H, Ar H), 8.94 (br s, 1 H, NH)
^{13}C NMR ($CDCl_3$): δ 12.56, 19.86, 71.59, 76.06, 117.38, 127.86, 128.10, 128.47, 136.73, 138.06, 151.18, 163.70

Preparative Example 12 :

Preparation of 1-[(benzyloxy)methyl]-5-isopropyluracil (a compound of the general formula (V) wherein R^1=$CH(CH_3)_2$, R^2=C_6H_5 and X=O)

[0033] The titled compound was prepared in the same manner as described in Preparative Example 9 by using 5-isopropyluracil and benzyl chloromethyl ether in place of 5-ethyluracil and chloromethyl ethyl ether, respectively.
Yield : 96%
IR (KBr) : 3404, 1708, 1654 cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 1.15 (d, *J* = 6.9 Hz, 6 H, $CH(CH_3)_2$), 2.89 (septet, *J* = 6.9 Hz, 1 H, $CH(CH_3)_2$), 4.64 (s, 2 H, CH_2Ph), 5.23 (s, 2 H, NCH_2O), 7.01 (s, 1 H, H-6), 7.30-7.40 (m, 5 H, Ar H), 8.64 (br s, 1 H, NH)
^{13}C NMR ($CDCl_3$): δ 21.45, 25.70, 71.68, 76.20, 121.81, 127.88, 128.14, 128.51, 136.75, 137.20, 150.94, 163.20

Preparative Example 13 :

Preparation of 1-[[2-(*tert*-butyldimethylsiloxy)ethoxy]methyl]-5-ethyl-2-thiouracil (a compound of the general formula (VI) wherein R^1=C_2H_5, W=(*tert*-butyldimethylsiloxy)-methyl and X=S)

[0034] A strirred suspension of 5-ethyl-2-thiouracil (6.00 g, 38.4 mmol) and $(NH_4)_2SO_4$ (0.80 g) in 1,1,1,3,3,3-hexamethyldisilazane (110 mL) was heated at reflux for 16 h under a nitrogen atmosphere. Volatile materials were evaporated *in vacuo* with protection against moisture. The residual oil was dissolved in MeCN (300 mL), and to this solution cooled to -60 °C were added [2-(trimethylsiloxy)ethoxy]methyl iodide, which was *in situ* generated from 1,3-dioxolane (3.41 g, 46.1 mmol, 3.2 mL) and iodotrimethylsilane (8.45 g, 42.2 mmol, 6.0 mL) in cyclohexene (20 mL) at -78 °C for 15 min under a nitrogen atmosphere, and CsI (10.00 g, 38.4 mmol). The mixture was slowly allowed to warm to room temperature and stirred for 3 h under a nitrogen atmosphere. The reaction mixture was poured into saturated $NaHCO_3$ solution (100 mL) and it was then extracted by using continuous extractor with CH_2Cl_2. The CH_2Cl_2 was solution dried over anhydrous $MgSO_4$ and evaporated to dryness to give 3.02 g of a residue. To a stirred solution of the residue in DMF (40 mL) were added imidazole (1.07 g, 15.74 mmol) and *tert*-butyldimethylsilyl chloride (2.37 g, 15.74 mmol), and the mixture was stirrred at room temperature for 16 h. The reaction mixture was poured into H_2O (100 mL) and it was then extracted with EtOAc (3 X 100 mL). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel with EtOAc-hexane (1:3) as eluent to give 4.74 g (36%) of the target compound,

IR (KBr) : 3230, 1698 cm^{-1}.
^1H NMR ($CDCl_3$/TMS): δ 0.08 (s, 6 H, $Si(CH_3)_2$), 0.90 (s, 9 H, $SiC(CH_3)_3$), 1.16 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 2.41 (q, J = 7.5 Hz, 2 H, CH_2CH_3), 3.72 (m, 2 H, CH_2OSi), 3.79 (m, 2 H, OCH_2), 5.66 (s, 2 H, NCH_2O), 7.29 (s, 1 H, H-6), 9.57 (br s, 1 H, NH)

Preparative Example 14 :

Preparation of 1-[[2-(*tert*-butyldimethylsiloxy)ethoxy]methyl]-5-isopropyl-2-thiouracil (a compound of the general formula (VI) wherein R^1=$CH(CH_3)_2$, W=(*tert*-butyldimethylsiloxy)methyl and X=S)

[0035] The titled compound was prepared in the same manner as described in Preparative Example 13 by using 5-isopropyl-2-thiouracil in place of 5-ethyl-2-thiouracil.
Yield : 33%
IR (KBr) : 3226, 1694 cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 0.08 (s, 6 H, $Si(CH_3)_2$), 0.90 (s, 9 H, $SiC(CH_3)_3$), 1.18 (d, J = 6.9 Hz, 6 H, $CH(CH_3)_2$), 2.93 (septet, J = 6.9 Hz, 1 H, $CH(CH_3)_2$), 3.73 (m, 2 H, CH_2OSi). 3.79 (m, 2 H, OCH_2), 5.67 (s, 2 H, NCH_2O), 7.24 (s, 1 H, H-6), 9.61 (br s, 1 H, NH)

Preparative Example 15 :

Preparation of 1-[[2-(*tert*-butyldimethylsiloxy)ethoxy]methyl]-5-ethyluracil (a compound of the general formula (VI) wherein R^1=C_2H_5, W=(*tert*-butyldimethylsiloxy)-methyl and X=O)

[0036] A suspension of 5-ethyluracil (4.50 g, 32.1 mmol) and *N,O*-bis(trimethylsilyl)acetamide (14.37 g, 70.6 mmol, 17.5 mL) in CH_2Cl_2 (40 mL) was stirred at room temperature for 2 h under a nitrogen atmosphere. To the resulting solution cooled to -60 °C was added [2-(trimethylsiloxy)ethoxy]methyl iodide which was *in situ* generated from 1,3-dioxolane (2.85 g, 38.5 mmol, 2.7 mL) and iodotrimethylsilane (7.07 g, 35.3 mmol, 5.0 mL) in cyclohexene (20 mL) at -78 °C for 15 min under a nitrogen atmosphere. The mixture was allowed to warm to room temperature over 30 min and stirred for 3 h under a nitrogen atmosphere. The reaction mixture was poured into saturated $NaHCO_3$ solution (80 mL) and it was then extracted by using continuous extractor with CH_2Cl_2. The CH_2Cl_2 solution was dried over anhydrous $MgSO_4$ and evaporated to dryness to give 6.20 g of a residue. To a stirred solution of the residue in DMF (80 mL) were added imidazole (2.62 g, 38.5 mmol) and *tert*-butyldimethylsilyl chloride (5.81 g, 38.5 mmol), and the mixture was stirred at room temperature for 16 h. The reaction mixture was poured into H_2O (200 mL) and it was then extracted with EtOAc (3 X 200 mL). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, and evaporated to dryness; The residue was purified by flash column chromatography on silica gel with EtOAc-hexane (1:1) as eluent to give 7.45 g (71%) of the target compound. IR (KBr): 3231, 1689 cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 0.06 (s, 6 H, $Si(CH_3)_2$), 0.89 (s, 9 H, $SiC(CH_3)_3$), 1.14 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 2.37 (q, J = 7.4 Hz, 2 H, CH_2CH_3), 3.65 (m, 2 H, CH_2OSi), 3.77 (m, 2 H, OCH_2), 5.21 (s, 2 H, NCH_2O), 7.11 (s, 1 H, H-6), 9.50 (br s, 1 H, NH)
^{13}C NMR ($CDCl_3$): δ -5.33, 12.60, 18.29, 19.90, 25.84, 62.36, 71.01, 76.77, 117.29, 138.12, 151.16, 163.79

Preparative Example 16:

Preparation of 1-[[2-(*tert*-butyldimethylsiloxy)ethoxy]methyl]-5-isopropyluracil (a compound of the general formula (VI) wherein R^1=$CH(CH_3)_2$, W=(*tert*-butyldimethylsiloxy)methyl and X=O)

[0037] The titled compound was prepared in the same manner as described in Preparative Example 15 by using 5-isopropyluracil in place of 5-ethyluracil.
Yield: 87%
IR (KBr) : 3270, 3221, 1688 cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 0.07 (s, 6 H, $Si(CH_3)_2$), 0.89 (s, 9 H, $SiC(CH_3)_3$), 1.16 (d, J = 6.9 Hz, 6 H, $CH(CH_3)_2$), 2.92 (septet, J = 6.9 Hz, 1 H, $CH(CH_3)_2$), 3.65 (m, 2 H, CH_2OSi), 3.77 (m, 2 H, OCH_2), 5.21 (s, 2 H, NCH_2O), 7.07 (s, 1 H, H-6), 9.18 (br s, 1 H, NH)
^{13}C NMR ($CDCl_3$): δ -5.28, 18.33, 21.46, 25.75, 25.89, 62.42, 71.11, 76.94, 121.74, 137.29, 150.95, 163.31

Preparative Example 17 :

Preparation of 3,3-(dimethylthio)-2-ethylacrylic acid (a compound of the general formula (IX) wherein $R^1 = C_2H_5$)

[0038] A mixture of ethyl 3,3-(dimethylthio)-2-ethylacrylate (300 mmol) and 2N KOH (300 mL) in EtOH (300 mL) was heated under reflux for 3 h. The reaction mixture was concentrated to remove EtOH and poured into H_2O (300 mL). The aqueous phase was washed with Et_2O (200 mL X 2), acidified with concentrated HCl to pH 3, and extracted with Et_2O (200 mL X 3). The combined ethereal solution was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was crystallized from hexane to give the titled compound as white crystals.
Yield : 86%
IR (KBr) : 1690 (CO) cm^{-1}
^1H NMR ($CDCl_3$/TMS) : δ 1.10 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 2.37 (s, 6 H, 2 SCH_3), 2.69 (q, J = 7.5 Hz, 2 H, CH_2CH_3), 11.48 (br s, 1 H, COOH)

Preparative Example 18 :

Preparation of 3,3-(dimethylthio)-2-isopropylacrylic acid (a compound of the general formula (IX) wherein R^1=CH $(CH_3)_2$)

[0039] The titled compound was prepared in the similar manner as described in Preparative Example 17 by using ethyl 3,3-(dimethylthio)-2-isopropylacrylate in place of ethyl 3,3-(dimethylthio)-2-ethylacrylate.
Yield: 82%
IR (KBr) : 1690 (CO) cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 1.15 (d, J = 6.9 Hz, 6 H, 2 CH_3), 2.29 (s, 3 H, SCH_3), 2.34 (s, 3 H, SCH_3), 3.34 (septet, J = 6.9 Hz, 1 H, CH)

Preparative Example 19:

Preparation of 3,3-(dimethylthio)-2-ethylacryloyl chloride (a compound of the general formula (X) wherein $R^1=C_2H_5$)

[0040] To a stirred solution of 3,3-(dimethylthio)-2-ethylacrylic acid (100 mmol) in anhydrous benzene (100 mL) were added oxalyl chloride (10.5 mL, 120 mmol) dropwise and 3 drops of DMF at 0 °C under a nitrogen atmosphere. The mixture was stirred at room temperature for 3 h and evaporated to dryness. The residue was distilled *in vacuo* to give the titled compound as a brick red oil.
Yield: 91%
IR (neat) : 1786 (CO) cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 1.14 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 2.37 (s, 3 H, SCH_3), 2.40 (s, 3 H, SCH_3), 2.72 (q, J = 7.5 Hz, 2 H, CH_2CH_3)

Preparative Example 20 :

Preparation of 3,3-(dimethylthio)-2-isopropylacryloyl chloride (a compound of the general formula (X) wherein R^1=CH $(CH_3)_2$)

[0041] The titled compound was prepared in the same manner as described in Preparative Example 19 by using 3,3-(dimethylthio)-2-isopropylacrylic acid in place of 3,3-(dimethylthio)-2-ethylacrylic acid.
Yield:91%
IR (neat): 1786 (CO) cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 1.18 (d, J = 6.9 Hz, 6 H, 2 CH_3), 2.32 (s, 3 H, SCH_3), 2.36 (s, 3 H, SCH_3), 3.32 (septet, J = 6.9 Hz, 1 H, CH)

Preparative Example 21 :

Preparation of *N*-butyl-*N'*-[3,3-(dimethylthio)-2-ethylacryloyl]urea (a compound of the general formula (XIa) wherein $R^1=C_2H_5$, $R^2=CH_3$ and X=O)

[0042] A mixture of 3,3-(dimethylthio)-2-ethylacryloyl chloride (3.50 g, 16.6 mmol) and AgOCN (2.61 g, 17.4 mmol) in anhydrous benzene (30 mL) was heated under reflux for 30 min under a nitrogen atmosphere in the dark to generate

isocyanate *in situ* and cooled to -78 °C. To this mixture was added butylamine (1.81 mL, 18.3 mmol) in anhydrous benzene (10 mL) in a dropwise manner. The mixture was allowed to warm to room temperature over 30 min and filtered through a pad of Celite, and the filtrate was again filtered using a millipore filter (0.22 *mm*). The filtrate was evaporated to dryness and the residue was purified by flash column chromatography on silica gel with EtOAc-hexane (1:6) as eluent to give 4.21 g of the titled compound.
Yield: 87%
IR (KBr) : 1665, 1690 (CO) cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 0.94 (t, *J* = 7.2 Hz, 3 H, $NCH_2CH_2CH_2CH_3$), 1.07 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 1.39 (m, 2 H, $NCH_2CH_2CH_2$), 1.58 (m, 2 H, NCH_2CH_2), 2.31 (s, 3 H, SCH_3), 2.34 (s, 3 H, SCH_3), 2.62 (q, *J* = 7.5 Hz, 2 H, CH_2CH_3), 3.31 (m, 2 H, NCH_2), 8.27 (br s, 2 H, 2 NH)
^{13}C NMR($CDCl_3$): δ 12.90, 13.71, 16.37, 17.71, 20.14, 27.22, 30.23, 45.51, 139.02, 142.35, 168.94, 179.52

Preparative Example 22 :

Preparation of *N*-[3,3-(dimethylthio)-2-ethylacryloyl]-*N'*-(3-phenylpropyl)urea (a compound of the general formula (XIa) wherein $R^1=C_2H_5$, R^2=Ph and X=O)

[0043] The titled compound was prepared in the same manner as described in Preparative Example 21 by using 3-phenyl-1-propylamine in place of butylamine.
Yield:91%
IR (KBr): 1662, 1698 (CO) cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 1.06 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 1.92 (quintet, *J* = 7.5 Hz, 2 H, NCH_2CH_2), 2.30 (s, 3 H, SCH_3), 2.32 (s, 3 H, SCH_3), 2.57-2.73 (m, 4 H, CH_2Ph and CH_2CH_3), 3.33 (dd, *J* = 12.9 Hz, *J* = 6.9 Hz, 2 H, NCH_2), 7.12-7.33 (m, 5 H, Ar H), 8.37 (br s, 1 H, NH), 8.49 (br s, 1 H, NH)
^{13}C NMR ($CDCl_3$): δ 12.83, 16.34, 17.46, 27.07, 31.09, 33.11, 39.37, 125.91, 128.34, 128.38, 136.49, 141.29, 143.91, 153.90, 170.50

Preparative Example 23:

Preparation of *N*-butyl-*N'*-[3,3-(dimethylthio)-2-isopropylacryloyl]urea (a compound of the general formula (XIa) wherein $R^1=CH(CH_3)_2$, $R^2=CH_3$ and X=O)

[0044] The titled compound was prepared in the same manner as described in Preparative Example 21 by using 3,3-(dimethylthio)-2-isopropylacryloyl chloride in place of 3,3-(dimethylthio)-2-ethylacryloyl chloride.
Yield : 84%
IR (KBr): 1674, 1696 (CO) cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 0.94 (t, *J* = 7.2 Hz, 3 H, $NCH_2CH_2CH_2CH_3$), 1.11 (d, *J* = 6.9 Hz, 6 H, $CH(CH_3)_2$), 1.38 (m, 2 H, $NCH_2CH_2CH_2$), 1.57 (m, 2 H, NCH_2CH_2), 2.26 (s, 3 H, SCH_3), 2.32 (s, 3 H, SCH_3), 3.23-3.40 (m, 3 H, NCH_2 and $CH(CH_3)_2$), 8.32 (br s, 1 H, NH), 8.83 (br s, 1 H, NH)
^{13}C NMR ($CDCl_3$):δ 13.75, 16.25, 17.31, 20.09, 21.12, 31.58, 32.34, 39.61, 133.79, 149.14, 153.83, 169.59

Preparative Example 24:

Preparation of *N*-[3,3-(dimethylthio)-2-isopropylacryloyl]-*N'*-(3-phenylpropyl)-urea (a compound of the general formula (XIa) wherein $R^1=CH(CH_3)_2$, R^2=Ph and X=O)

[0045] The titled compound was prepared in the same manner as described in Preparative Example 21 by using 3,3-(dimethylthio)-2-isopropylacryloyl chloride and 3-phenyl-1-propylamine in place of 3,3-(dimethylthio)-2-ethylacryloyl chloride and butylamine, respectively.
Yield: 88%
IR (KBr):1675, 1695 (CO) cm^{-1}
^1H NMR ($CDCl_3$/TMS) : δ 1.11 (d, *J* = 6.9 Hz, 6 H, $CH(CH_3)_2$), 1.92 (quintet, *J* = 7.5 Hz, 2 H, NCH_2CH_2), 2.26 (s, 3 H, SCH_3), 2.31 (s, 3 H, SCH_3), 2.69 (t, *J* = 7.8 Hz, 2 H, CH_2Ph), 3.25-3.40 (m, 3 H, NCH_2 and $CH(CH_3)_2$), 7.15-7.33 (m, 5 H, Ar H), 8.38 (br s, 1 H, NH), 8.58 (br s, 1 H, NH)
^{13}C NMR ($CDCl_3$) : δ 16.24, 17.35, 21.14, 31.10, 32.33, 33.10, 39.36, 125.93, 128.36, 128.40, 133.99, 141.30, 148.99, 153.71, 169.57

Preparative Example 25:

Preparation of *N*-[3,3-(dimethylthio)-2-ethylacryloyl]-*N'*-(4-hydroxybutyl) thiourea (a compound of the general formula (XIb) wherein $R^1=C_2H_5$, $R^2=CH_2OH$ and X=S)

[0046] A mixture of 3,3-(dimethylthio)-2-ethylacryloyl chloride (5.20 g, 24.7 mmol) and NH_4SCN (1.97 g, 25.9 mmol) in anhydrous benzene (30 mL) was heated under reflux for 30 min under a nitrogen atmosphere in the dark to generate thioisocyanate *in situ* and cooled to 0 °C. To this mixture was added 4-amino-1-butanol (2.50 mL, 27.2 mmol) in anhydrous benzene (10 mL) in a dropwise manner. After stirred at room temperature for 1 h, the mixture was poured into H_2O (40 mL) and extracted with EtOAc (50 mL X 3). The combined organic phase was washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel with EtOAc-hexene (1 : 2) as eluent to give 6.39 g of the titled compound.
Yield : 80%
IR (KBr) : 1663 (CO), 3385 (OH) cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 1.07 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 1.55 (br s, 1 H, OH), 1.67 (m, 2 H, $NCH_2CH_2CH_2$), 1.82 (m, 2 H, NCH_2CH_2), 2.36 (s, 6 H, 2 SCH_3), 2.63 (q, *J* = 7.5 Hz, 2 H, CH_2CH_3), 3.62-3.80 (m,. 4 H, NCH_2 and CH_2OH), 8.96 (br s, 1 H, NH), 10.47 (br s, 1 H, NH)
^{13}C NMR ($CDCl_3$): δ 12.87, 16.34, 17.65, 24.65, 27.18, 29.76, 45.29, 62.11, 138.94, 142.31, 169.01, 179.70

Preparative Example 26 :

Preparation of *N*-butyl-*N'*-[3,3-(dimethylthio)-2-ethylacryloyl]thiourea (a compound of the general formula (XIb) wherein $R^1=C_2H_5$, $R^2=CH_3$ and X=S)

[0047] The titled compound was prepared in the same manner as described in Preparative Example 25 by using butylamine in place of 4-amino-1-butanol.
Yield: 85%
IR (KBr) : 1671 (CO) cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 0.97 (t, *J* = 7.2 Hz, 3 H, $NCH_2CH_2CH_2CH_3$), 1.07 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 1.43 (m, 2 H, $NCH_2CH_2CH_2$), 1.68 (m, 2 H, NCH_2CH_2), 2.35 (s, 3 H, SCH_3), 2.36 (s, 3 H, SCH_3), 2.63 (q, *J* = 7.5 Hz, 2 H, CH_2CH_3), 3.66 (m, 2 H, NCH_2), 9.15 (br s, 1 H, NH), 10.43 (br s, 1 H, NH)
^{13}CNMR($CDCl_3$): δ 12.90, 13.71, 16.37, 17.70, 20.14, 27.22, 30.24, 45.50, 138.99, 142.38, 168.96, 179.54

Preparative Example 27 :

Preparation of *N*-[3,3-(dimethylthio)-2-isopropylacryloyl]-*N'*-(4-hydroxybutyl) thiourea (a compound of the general formula (XIb) wherein $R^1=CH(CH_3)_2$, $R^2=CH_2OH$ and X=S)

[0048] The titled compound was prepared in the same manner as described in Preparative Example 25 by using 3,3-(dimethylthio)-2-isopropylacryloyl chloride in place of 3,3-(dimethylthio)-2-ethylacryloyl chloride.
Yield : 77%
IR (KBr) : 1666 (CO), 3253 (OH) cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 1.13 (d, *J* = 6.9 Hz, 6 H, $CH(CH_3)_2$), 1.60-1.73 (m, 2 H, $NCH_2CH_2CH_2$), 1.82 (m, 2 H, NCH_2CH_2), 2.31 (s, 3 H, SCH_3), 2.35 (s, 3 H, SCH_3), 3.33 (septet, *J* = 6.9 Hz, 1 H, $CH(CH_3)_2$), 3.64-3.76 (m, 4 H, NCH_2 and CH_2OH), 8.84 (br s, 1 H, NH), 10.46 (br s, 1 H, NH)
^{13}C NMR ($CDCl_3$): δ 16.19, 17.41, 21.08, 24.67, 29.79, 32.54, 45.34, 62.18, 135.71, 147.80, 168.56, 179.60

Preparative Example 28 :

Preparation of *N*-butyl-*N'*-[3,3-(dimethylthio)-2-isopropylacryloyl]thiourea (a compound of the general formula (XIb) wherein $R^1=CH(CH_3)_2$, $R^2=CH_3$ and X=S)

[0049] The titled compound was prepared in the same manner as described in Preparative Example 25 by using 3,3-(dimethylthio)-2-isopropylacryloyl chloride and butylamine in place of 3,3-(dimethylthio)-2-ethylacryloyl chloride and 4-amino-1-butanol, respectively. Yield: 81%
IR (KBr) : 1670 (CO) cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 0.97 (t, *J* = 7.4 Hz, 3 H, $NCH_2CH_2CH_2CH_3$), 1.13 (d, *J* = 6.9 Hz, 6 H, $CH(CH_3)_2$), 1.43 (m, 2 H, $NCH_2CH_2CH_2$), 1.69 (m, 2 H, NCH_2CH_2), 2.31 (s, 3 H, SCH_3), 2.35 (s, 3 H, SCH_3), 3.33 (septet, *J* = 6.9 Hz, 1 H,

$CH(CH_3)_2$), 3.66 (m, 2 H, NCH_2), 8.80 (br s, 1 H, NH), 10.40 (br s, 1 H, NH)
^{13}C NMR ($CDCl_3$): δ 13.73, 16.19, 17.40, 20.14, 21.08, 30.22, 32.54, 45.51, 135.65, 147.85, 168.57, 179.43

Preparative Example 29 :

Preparation of 1-butyl-5-ethyl-6-(methylthio)uracil (a compound of the general formula (XII) wherein $R^1=C_2H_5$ and $R^2=CH_3$)

[0050] A stirred suspension of N-butyl-N'-[3,3-(dimethylthio)-2-ethylacryloyl]urea (0.50 g, 1.72 mmol) and methanesulfonic acid (25.0 mg, 0.26 mmol) in AcOH (10 mL) was heated at 80 °C for 1 h. The reaction mixture was evaporated to dryness and the residue was dissolved in CH_2Cl_2 (50 mL). The CH_2Cl_2 solution was washed with saturated $NaHCO_3$ solution (25 mL) and brine (25 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel with EtOAc-hexane (1 : 3) as eluent to give 0.40 g of the titled compound.
Yield: 96%
IR (KBr):1663, 1682 (CO) cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 0.96 (t, *J* = 7.4 Hz, 3 H, $NCH_2CH_2CH_2CH_3$), 1.13 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 1.38 (m, 2 H, $NCH_2CH_2CH_2$), 1.65 (m, 2H, NCH_2CH_2), 2.41 (s, 3 H, SCH_3), 2.71 (q, *J* = 7.5 Hz, 2 H, CH_2CH_3), 4.13 (t, *J* = 7.8 Hz, 2 H, NCH_2), 8.66 (br s, 1 H, NH) ^{13}C NMR ($CDCl_3$): δ 13.73, 14.07, 19.88, 20.08, 22.23, 31.47, 46.53, 124.01, 149.20, 150.74, 162.10

Preparative Example 30 :

Preparation of 5-ethyl-6-(methylthio)-1-(3-phenylpropyl)uracil (a compound of the general formula (XII) wherein $R^1=C_2H_5$ and R^2=Ph)

[0051] The titled compound was prepared in the same manner as described in Preparative Example 29 by using *N*-[3,3-(dimethylthio)-2-ethylacryloyl]-*N*'-(3-phenylpropyl)urea in place of *N*-butyl-*N*'-[3,3-(dimethylthio)-2-ethylacryloyl] urea.
Yield : 93%
IR (KBr):1667 (CO) cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 1.11 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 2.03 (tt, *J* = 7.8 Hz, *J* = 7.5 Hz, 2 H, NCH_2CH_2), 2.32 (s, 3 H, SCH_3), 2.67 (t, *J* = 7.5 Hz, 2 H, CH_2Ph), 2.70 (q, *J* = 7.5 Hz, 2 H, CH_2CH_3), 4.16 (t, *J* = 7.8 Hz, 2 H, NCH_2), 7.19-7.31 (m, 5 H, Ar H), 8.90 (br s, 1 H, NH)
^{13}C NMR ($CDCl_3$): δ 14.05, 19.97, 22.24, 30.52, 32.88, 46.36, 124.10, 126.06, 128.26, 128.39, 140.76, 149.00, 150.61, 161.86

Preparative Example 31 :

Preparation of 1-butyl-5-isopropyl-6-(methylthio)uracil (a compound of the general formula (XII) wherein $R^1=CH(CH_3)_2$ and $R^2=CH_3$)

[0052] The titled compound was prepared in the same manner as described in Preparative Example 29 by using *N*-butyl-*N*'-[3,3-(dimethylthio)-2-isopropylacryloyl]urea in place of *N*-butyl-*N*'-[3,3-(dimethylthio)-2-ethylacryloyl]urea.
Yield : 84%
IR (KBr) : 1646, 1699 (CO) cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 0.96 (t, *J* = 7.4 Hz, 3 H, $NCH_2CH_2CH_2CH_3$), 1.33 (d, *J* = 6.9 Hz, 6 H, $CH(CH_3)_2$), 1.39 (m, 2 H, $NCH_2CH_2CH_2$), 1.64 (m, 2 H, NCH_2CH_2), 2.40 (s, 3 H, SCH_3), 3.54 (septet, *J* = 6.9 Hz, 1 H, $CH(CH_3)_2$), 4.15 (t, *J* = 7.8 Hz, 2 H, NCH_2), 8.77 (br s, 1 H, NH)
^{13}C NMR ($CDCl_3$): δ 13.75, 19.88, 20.25, 20.55, 31.59, 31.70, 46.66, 126.39, 149.13, 150.58, 161.20

Preparative Example 32:

Preparation of 5-isopropyl-6-(methylthio)-1-(3-phenylpropyl)uracil (a compound of the general formula (XII) wherein $R^1=CH(CH_3)_2$ and R^2=Ph)

[0053] The titled compound was prepared in the same manner as described in Preparative Example 29 by using *N*-[3,3-(dimethylthio)-2-isopropylacryloyl]-*N*'-(3-phenylpropyl) urea in place of *N*-butyl-*N*'-[3,3-(dimethylthio)-2-ethyl-

acryloyl]urea.
Yield: 86%
IR (KBr) : 1682, 1694 (CO) cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 1.31 (d, J = 6.9 Hz, 6 H, $CH(CH_3)_2$), 2.01 (tt, J = 7.8 Hz, J = 7.7 Hz, 2 H, NCH_2CH_2), 2.32 (s, 3 H, SCH_3), 2.70 (t, J = 7.7 Hz, 2 H, CH_2Ph), 3.51 (septet, J = 6.9 Hz, 1 H, $CH(CH_3)_2$), 4.18 (t, J = 7.8 Hz, 2 H, NCH_2), 7.16-7.31 (m, 5 H, Ar H), 8.55 (br s, 1 H, NH)
^{13}C NMR ($CDCl_3$): δ 20.16, 20.53, 30.71, 31.68, 32.88, 46.49, 126.05, 126.53, 128.26, 128.38, 140.82, 148.89, 150.51, 161.04

Preparative Example 33 :

Preparation of 1-butyl-5-ethyl-6-(methylsulfonyl)uracil (a compound of the general formula (XIII) wherein R^1=C_2H_5 and R^2=CH_3)

[0054] A mixture of 1-butyl-5-ethyl 6-(methylthio)uracil (1.50 g, 6.2 mmol) and 3-chloroperoxybenzoic acid (85%, 6.29 g, 31.0 mmol) in benzene (50 mL) was heated under reflux for 16 h. The reaction mixture was evaporated to dryness and the residue was dissolved in H_2O (50 mL). The aqueous phase was extracted with EtOAc (50 mL X 3). The combined EtOAc solution was washed with saturated $NaHCO_3$ solution (50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel with EtOAc-hexane (1 : 2) as eluent to give 1.67 g of the titled compound.
Yield : 98%
IR (KBr) : 1149 (SO_2), 1688 (CO) cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 0.95 (t, J = 7.4 Hz, 3 H, $NCH_2CH_2CH_2CH_3$), 1.19 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 1.36 (m, 2 H, $NCH_2CH_2CH_2$), 1.72 (m, 2 H, NCH_2CH_2), 2.90 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 3.23 (s, 3 H, SO_2CH_3), 4.21 (t, J = 7.8 Hz, 2 H, NCH_2), 9.17 (br s, 1 H, NH)
^{13}C NMR ($CDCl_3$): δ 13.62, 14.35, 19.87, 20.42, 31.55, 45.32, 47.61, 124.52, 147.94, 150.10, 162.07

Preparative Example 34 :

Preparation of 5-ethyl-6-(methylsulfonyl)-1-(3-phenylpropyl)uracil (a compound of the general formula (XIII) wherein R^1=C_2H_5 and R^2=Ph)

[0055] The titled compound was prepared in the same manner as described in Preparative Example 33 by using 5-ethyl-6-(methylthio)-1-(3-phenylpropyl)uracil in place of 1-butyl-5-ethyl-6-(methylthio)uracil.
Yield : 93%
IR (KBr): 1150 (SO_2), 1690 (CO) cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 1.17 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 2.10 (tt, J = 7.8 Hz, J = 7.7 Hz, 2 H, NCH_2CH_2), 2.69 (t, J = 7.7 Hz, 2 H, CH_2Ph), 2.86 (q, J = 7.4 Hz, 2 H, CH_2CH_3), 3.10 (s, 3 H, SO_2CH_3), 4.23 (t, J = 7.8 Hz, 2 H, NCH_2), 7.18-7.33 (m, 5 H, Ar H), 9.01 (br s, 1 H, NH)
^{13}C NMR ($CDCl_3$): δ 14.30, 20.43, 30.70, 32.82, 45.13, 47.46, 124.66, 126.11, 128.35, 128.43, 140.59, 147.80, 150.21, 162.15

Preparative Example 35 :

Preparation of 1-butyl-5-isopropyl-6-(methylsulfonyl)uracil (a compound of the general formula (XIII) wherein R^1=$CH(CH_3)_2$ and R^2=CH_3)

[0056] The titled compound was prepared in the same manner as described in Preparative Example 33 by using 1-butyl-5-isopropyl-6-(methylthio)uracil in place of 1-butyl-5-ethyl-6-(methylthio)uracil.
Yield : 88%
IR (KBr): 1154 (SO_2), 1676, 1696 (CO) cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 0.95 (t, J = 7.4 Hz, 3 H, $NCH_2CH_2CH_2CH_3$), 1.34 (m, 2 H, $NCH_2CH_2CH_2$), 1.38 (d, J = 6.9 Hz, 6 H, $CH(CH_3)_2$), 1.73 (m, 2 H, NCH_2CH_2), 3.26 (s, 3 H, SO_2CH_3), 3.76 (septet, J = 6.9 Hz, 1 H, $CH(CH_3)_2$), 4.21 (t, J = 7.8 Hz, 2 H, NCH_2), 8.92 (br s, 1 H, NH)
^{13}C NMR ($CDCl_3$): δ 13.63, 19.90, 20.00, 28.92, 31.72, 45.99, 48.06, 127.52, 149.18, 150.36, 160.86

Preparative Example 36 :

Preparation of 5-isopropyl-6-(niethylsulfonyl)-1-(3-phenylpropyl)uracil (a compound of the general formula (XIII) wherein R^1=$CH(CH_3)_2$ and R^2=Ph)

[0057] The titled compound was prepared in the same manner as described in Preparative Example 33 by using 5-isopropyl-6-(methylthio)-1-(3-phenylpropyl)uracil in place of 1-butyl-5-ethyl-6-(methylthio)uracil.
Yield : 95%
IR (KBr): 1154 (SO_2), 1688 (CO) cm^{-1}
^{1}H NMR ($CDCl_3$/TMS): δ 1.37 (d, *J* = 6.9 Hz, 6 H, $CH(CH_3)_2$), 2.11 (quintet, *J*= 7.7 Hz, 2 H, NCH_2CH_2), 2.67 (t, *J* = 7.7 Hz, 2 H, CH_2Ph), 3.13 (s, 3 H, SO_2CH_3), 3.72 (septet, *J* = 6.9 Hz, 1 H, $CH(CH_3)_2$), 4.22 (t, *J* = 7.7 Hz, 2 H, NCH_2), 7.14-7.33 (m, 5 H, Ar H), 8.85 (br s, 1 H, NH)
^{13}C NMR ($CDCl_3$): δ 20.01, 28.99, 30.94, 32.92, 45.76, 48.03, 126.12, 127.75, 128.38, 128.45, 140.68, 149.09, 150.30, 160.76

Preparative Example 37 :

Preparation of 1-(4-acetoxybutyl)-5,6-dihydro-6-(dimethylthio)-5-ethyl-2-thiouracil (a compound of the general formula (XIV) wherein R^1=C_2H_5 and R^2=CH_2OAc)

[0058] A suspension of *N*-[3,3-(dimethylthio)-2-ethylacryloyl]-*N*'-(4-hydroxybutyl) thiourea (4.50 g, 14.0 mmol) and methanesulfonic acid (1.35 g, 14.0 mmol) in AcOH (50 mL) was stirred at room temperature for 1.5 h. The reaction mixture was evaporated to dryness and the residue was dissolved in CH_2Cl_2 (150 mL). The CH_2Cl_2 solution was washed with saturated $NaHCO_3$ solution (50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel with EtOAc-hexane (4:1) as eluent to give 4.50 g of the titled compound as an oil.
Yield: 88%
IR (neat):1648 (CO),1737 (CO_2) cm^{-1}
^{1}H NMR ($CDCl_3$/TMS):δ 1.03 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.63-1.84 (m, 5 H, $NCH_2CH_2CH_2$ and 1 H of CH_2CH_3), 1.97-2.13 (m, 1 H, CH_2CH_3), 2.04 (s, 3 H, $COCH_3$), 2.16 (s, 3 H, SCH_3), 2.25 (s, 3 H, SCH_3), 2.75 (dd, *J* = 10.8 Hz, *J* = 3.6 Hz, 1 H, H-5), 3.40 (br s, 2 H, NCH_2), 4.08 (t, *J* = 5.4 Hz, 2 H, CH_2OAc)
^{13}C NMR ($CDCl_3$): δ 12.38, 12.61, 13.96, 20.90, 21.02, 25.94, 29.61; 43.97, 52.36, 63.94, 69.70, 163.17, 170.99, 175.51

Preparative Example 38 :

Preparation of 1-butyl-5,6-dihydro-6-(dimethylthio)-5-ethyl-2-thiouracil (a compound of the general formula (XIV) wherein R^1=C_2H_5 and R^2=CH_3)

[0059] The titled compound was prepared in the same manner as described in Preparative Example 37 by using *N*-butyl-*N*'-[3,3-(dimethylthio)-2-ethylacryloyl]thiourea in place of *N*-[3,3-(dimethylthio)-2-ethylacryloyl]-*N*'-(4-hydroxybutyl)thiourea.
Yield : 99%
IR (KBr):1652(CO)cm^{-1}
^{1}H NMR ($CDCl_3$/TMS): δ 0.93 (t, *J* = 7.4 Hz, 3 H, $NCH_2CH_2CH_2CH_3$), 1.04 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 1.37 (m, 2 H, $NCH_2CH_2CH_2$), 1.60 (m, 2 H, NCH_2CH_2), 1.74 (m, 1 H, CH_2CH_3), 2.03 (m, 1 H, CH_2CH_3), 2.16 (s, 3 H, SCH_3), 2.25 (s, 3 H, SCH_3), 2.77 (dd, *J* = 10.8 Hz, *J* = 3.6 Hz, 1 H, H-5), 3.33 (m, 2 H, NCH_2), 9.08 (br s, 1 H, NH)
^{13}C NMR ($CDCl_3$): δ 12.40, 12.63, 13.75, 13.99, 20.05, 21.06, 31.84, 44.16, 52.35, 69.75, 163.39, 175.74

Preparative Example 39 :

Preparation of 1-(4-acetoxybutyl)-5,6-dihydro-6-(dimethylthio)-5-isopropyl-2-thiouracil (a compound of the general formula (XIV) wherein R^1=$CH(CH_3)_2$ and R^2=CH_2OAc)

[0060] The titled compound was prepared in the same manner as described in Preparative Example 37 by using *N*-[3,3-(dimethylthio)-2-isopropylacryloyl]-*N*'-(4-hydroxybutyl)-thiourea in place of *N*-[3,3-(dimethylthio)-2-ethylacryloyl]-*N*'-(4-hydroxybutyl)thiourea. Yield : 94%
IR (KBr) : 1644 (CO). 1742 (CO_2) cm^{-1}
^{1}H NMR ($CDCl_3$/TMS): δ 1.04 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$), 1.19 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$), 1.69 (m, 4 H,

$NCH_2CH_2CH_2$), 2.05 (s, 3 H, $COCH_3$), 2.13 (s, 3 H, SCH_3), 2.25 (s, 3 H, SCH_3), 2.46 (m, 1 H, $CH(CH_3)_2$), 2. 82 (d, J = 2.7 Hz, 1 H, H-5), 3.36 (br s, 2 H, NCH_2), 4.08 (br s, 2 H, CH_2OAc)
^{13}C NMR ($CDCl_3$) : δ 12.79, 14.33, 20.14, 20.98, 25.01, 26.08, 26.67, 28.31, 45.98, 56.89, 64.10, 69.43, 156.74, 171.09; 172.39

Preparative Example 40 :

Preparation of 1-butyl-5,6-dihydro-6-(dimethylthio)-5-isopropyl-2-thiouracil (a compound of the general formula (XIV) wherein R^1=$CH(CH_3)_2$ and R^2=CH_3)

[0061] The titled compound was prepared in the same manner as described in Preparative Example 37 by using *N*-butyl-*N*'-[3,3-(dimethylthio)-2-isopropylacryloyl]thiourea in place of *N*-[3,3-(dimethylthio)-2-ethylacryloyl]-*N*'-(4-hydroxybutyl)thiourea.
Yield : 99%
IR (KBr) : 1633 (CO) cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 0.92 (t, J = 7.2 Hz, 3 H, $NCH_2CH_2CH_2CH_3$), 1.02 (d, J = 6.6 Hz, 3 H, $CHCH_3$), 1.18 (d, J = 6.6 Hz, 3 H, $CHCH_3$), 1.37 (m, 2 H, $NCH_2CH_2CH_2$), 1.60 (m, 2 H, NCH_2CH_2), 2.13 (s, 3 H, SCH_3), 2.25 (s, 3 H, SCH_3), 2.44 (m, 1 H, $CH(CH_3)_2$), 2.78 (d, J = 3.3 Hz, 1 H, H-5), 3.36 (br s, 2 H, NCH_2), 9.62 (br s, 1 H, NH)
^{13}C NMR ($CDCl_3$) : δ 12.64, 13.77, 14.21, 20.05, 20.17, 24.96, 28.11, 31.96, 44.63, 56.15, 69.84, 162.12, 174.35

Preparative Example 41 :

Preparation of 1-(4-acetoxybutyl)-5-ethyl-6-(methylsulfinyl)-2-thiouracil (a compound of the general formula (XV) wherein R^1=C_2H_5 and R^2=CH_2OAc)

[0062] To a stirred solution of 1-(4-acetoxybutyl)-5,6-dihydro-6-(dimethylthio)-5-ethyl-2-thiouracil (1.46 g, 4.0 mmol) in MeOH (50 mL) was added a solution of $NaIO_4$ (5.14 g, 24.0 mmol) in H_2O (50 mL) at room temperature. The mixture was heated under reflux for 1.5 h and filtered. The filtrate was concentrated to 50 mL in volume. The concentrate was extracted by using continuous extractor with $CHCl_3$. The $CHCl_3$ solution was dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel with MeOH-$CHCl_3$ (3 : 97) as eluent to give 0.77 g of the titled compound.
Yield : 70%
IR (KBr): 1054 (SO), 1630 (CO), 1734 (CO_2) cm^{-1}
^1H NMR($CDCl_3$/rMS): δ 1.15 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 1.73 (br s, 4 H, $NCH_2CH_2CH_2$), 2.06 (s, 3 H, $COCH_3$), 2.64 (m, 2 H, CH_2CH_3), 2.86 (s, 3 H, $SOCH_3$), 3.58 (br s, 2 H, NCH_2), 4.10 (t, J = 5.7 Hz, 2 H, CH_2OAc), 6.94(br s, 1 H, NH)

Preparative Example 42:

Preparation of 1-butyl-5-ethyl-6-(methylsulfinyl)-2-thiouracil (a compound of the general formula (XV) wherein R^1=C_2H_5 and R^2=CH_3)

[0063] The titled compound was prepared in the same manner as described in Preparative Example 41 by using 1-butyl-5,6-dihydro-6-(dimethylthio)-5-ethyl-2-thiouracil in place of 1-(4-acetoxybutyl)-5,6-dihydro-6-(dimethylthio)-5-ethyl-2-thiouracil.
Yield : 73%
IR (KBr) : 1042 (SO), 1633 (CO) cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 0.95 (t, J = 7.4 Hz, 3 H, $NCH_2CH_2CH_2CH_3$), 1.15 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 1.42 (m, 2 H, $NCH_2CH_2CH_2$), 1.65 (m, 2 H, NCH_2CH_2), 2.65 (m, 2 H, CH_2CH_3), 2.85 (s, 3 H, $SOCH_3$), 3.52 (br s, 2 H, NCH_2), 6.63 (br s, 1 H, NH)

Preparative Example 43 :

Preparation of 1-(4-acetoxybutyl)-5-isopropyl-6-(methylsulfinyl)-2-thiouracil (a compound of the general formula (XV) wherein R^1=$CH(CH_3)_2$ and R^2=CH_2OAc)

[0064] The titled compound was prepared in the same manner as described in Preparative Example 41 by using 1-(4-acetoxybutyl)-5,6-dihydro-6-(dimethylthio)-5-isopropyl-2-thiouracil in place of 1-(4-acetoxybutyl)-5,6-dihydro-6-(dimethylthio)-5-ethyl-2-thiouracil.

Yield : 57%
IR (KBr) : 1060 (SO), 1622 (CO), 1737 (CO_2) cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 1.36 (d, J = 7.5 Hz, 3 H, $CHCH_3$), 1.38 (d, J = 7.2 Hz, 3 H, $CHCH_3$), 1.73 (br s, 4 H, $NCH_2CH_2CH_2$), 2.05 (s, 3 H, $COCH_3$), 2.83 (s, 3 H, $SOCH_3$), 2.90 (septet, J = 6.6 Hz, 1 H, $CH(CH_3)_2$), 3.56 (br s, 2 H, NCH_2), 4.10 (t, J = 5.9 Hz, 2 H, CH_2OAc), 6.81 (br s, 1 H, NH)
^{13}C NMR ($CDCl_3$): δ 19.91, 20.66, 20.97, 25.59, 26.00, 32.96, 41.99, 42.46, 63.83, 136.05, 149.97, 152.43, 171.06

Preparative Example 44 :

Preparation of 1-butyl-5-isopropyl-6-(methylsulfinyl)-2-thiouracil (a compound of the general formula (XV) wherein R^1=$CH(CH_3)_2$ and R^2=CH_3)

[0065] The titled compound was prepared in the same manner as described in Preparative Example 41 by using 1-butyl-5,6-dihydro-6-(dimethylthio)-5-isopropyl-2-thiouracil in place of 1-(4-acetoxybutyl)-5,6-dihydro-6-(dimethylthio)-5-ethyl-2-thiouracil.
Yield : 63%
IR (KBr) : 1052 (SO), 1643 (CO) cm^{-1}
^1H NMR ($CDCl_3$/TMS): δ 0.94 (t, J = 7.2 Hz, 3 H, $NCH_2CH_2CH_2CH_3$), 1.36 (d, J = 7.8 Hz, 3 H, $CHCH_3$), 1.39 (d, J = 7.2 Hz, 3 H, $CHCH_3$), 1.41 (m, 2 H, $NCH_2CH_2CH_2$), 1.64 (m, 2 H, NCH_2CH_2), 2.83 (s, 3 H, $SOCH_3$), 2.90 (septet, J = 6.9 Hz,, 1 H, $CH(CH_3)_2$), 3.50 (br s, 2 H, NCH_2), 6.57 (br s, 1 H, NH)
^{13}C NMR ($CDCl_3$): δ 13.69, 19.92, 20.00, 20.67, 31.01, 32.94, 41.98, 42.71, 102.17, 136.14, 149.86, 152.42

Example 1 :

Preparation of 6-[(3,5-dimethylphenyl)selenenyl]-1-(ethoxymethyl)-5-etlyluracil (Compound No. **1**)

[0066] To a stirred solution of 1-(ethoxymethyl)-5-ethyluracil (0.20 g, 0.93 mmol) in anhydrous THF (6 mL) was added LDA (1.56 mL of 1.5M solution in cyclohexane, 2.33 mmol) dropwise under a nitrogen atmosphere, at a rate such that the temperature did not exceed -70°C. After the mixture was stirred for 1 h, bis(3,5-dimethylphenyl) diselenide (0.44 g, 1.41 mmol) dissolved in anhydrous THF (3 mL) was added dropwise. The mixture was stirred for 1 h below -70°C. The reaction mixture was quenched with AcOH (0.27 mL, 4.66 mmol), and then allowed to warm to room temperature. The suspension was partitioned between EtOAc (25 mL) and H_2O (25 mL). The aqueous phase was extracted with EtOAc (2 X 25 mL). The combined organic phase was washed with saturated $NaHCO_3$ solution (25 mL) and brine (25 mL), dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel with EtOAc-hexane (1:4) as eluent to give 0.23 g (89%) of the target compound.
Yield: 67%;
IR (KBr): 1709, 1646 cm^{-1} ;
^1H NMR($CDCl_3$/TMS): δ 0.94 (t, J=7.4 Hz, 3 H, CH_2CH_3), 1.16 (t, J=7.1 Hz, 3 H, OCH_2CH_3), 2.28 (s, 6 H, 2 CH_3), 2.68 (q, J=7.4 Hz, 2 H, CH_2CH_3), 3.58 (q, J=7.1 Hz, 2 H, OCH_2CH_3), 5.56 (s, 2 H, NCH_2O), 6.90 (s, 1 H, Ar H), 6.96 (s, 2 H, Ar H), 8.59 (br s, 1 H, NH)

Example 2 :

Preparation of 1-[(benzyloxy)methyl]-6-[(3,5-dimethylphenyl)selenenyl]-5-ethyluracil (Compound No. **2**)

[0067] The titled compound was prepared in the same manner as described in Example 1 by using 1-[(benzyloxy) methyl]-5-ethyluracil and bis(3,5-dimethylphenyl) diselenide in place of 1-(ethoxymethyl)-5-ethyluracil and bis (3,5-dimethylphenyl) diselenide, respectively.
Yield: 20%;
IR (KBr): 1708, 1667 cm^{-1} ;
^1H NMR($CDCl_3$/TMS): δ 0.92 (t, J=7.4 Hz, 3 H, CH_2CH_3), 2.24 (s, 6 H, 2 CH_3), 2.64 (q, J=7.4 Hz, 2 H, CH_2CH_3), 4.64 (s, 2 H, CH_2Ph), 5.64 (s, 2 H, NCH_2O), 6.88 (s, 1 H, Ar H), 6.91 (s, 2 H, Ar H), 7.24-7.35 (m, 5 H, Ar H), 8.30 (br s, 1 H, NH)

Example 3-A :

Preparation of 6-[(3,5-dimethylphenyl)selenenyl]-1-(ethoxymethyl)-5-isopropyluracil (Compound No. **3**)

[0068] To a stirred suspension of 6-[(3,5-dimethylphenyl)selenenyl]-1-(ethoxymethyl)-5-isopropyl-2-thiouracil (0.26

g, 0.68 mmol) in aqueous 1N NaOH (6 mL) was added 35% H_2O_2 (0.40 mL, 4.08 mmol). After the mixture was stirred at room temperature for 1 h, the reaction mixture was neutralized with concentrated HCl. The resulting precipitate was filtered and washed well with saturated $NaHCO_3$ solution (3 X 5 mL) and H_2O (3 X 5 mL). The precipitate was thoroughly dried in vacuo over P_2O_5 and crystallized from EtOAc-hexane to give 0.22 g (88%) of the target compound
Yield: 88%;
IR (KBr): 1711, 1645 cm^{-1} ;
^1H NMR($CDCl_3$/TMS): δ 1.09 (d, *J*=6.9 Hz, 6 H, $CH(CH_3)_2$), 1.18 (t, *J*=7.1 Hz, 3 H, OCH_2CH_3), 2.28 (s, 6 H, 2 CH_3), 3.43 (septet, *J*=6.9 Hz, 1 H, $CH(CH_3)_2$), 3.59 (q, *J*=7.1 Hz, 2 H, OCH_2CH_3), 5.64 (s, 2 H, NCH_2O), 6.90 (s, 1 H, Ar H), 6.99 (s, 2 H, Ar H), 8.43 (br s, 1 H, NH)

Example 3-B :

Preparation of 6-[(3,5-dimethylphenyl)selenenyll-1-(ethoxymethyl)-5-isopropyluracil (Compound No. **3**)

[0069] To a solution of 6-chloro-1-(ethoxymethyl)-5-isopropyluracil (1.00 g, 4.06 mmol) in absolute EtOH (15 mL) at room temperature under a nitrogen atmosphere was added 1 N ethanolic NaOH solution (4.26 mmol, 4.3. mL) followed by dropwise addition of 3,5-dimethylphenyl selenol (789 mg, 4.26 mmol, 0.61 mL) via a syringe and the resulting slurry was stirred at room temperature for 2 h. The reaction mixture was cooled to 0°C, a white precipitate was collected and was washed with cold EtOH. The resulting white solid was dissolved in CH_2Cl_2 and insoluble NaCl was removed by passing through a Celite pad. Evaporation to dryness gave a white crystalline product (1.31 g, 82%). The ethanolic portion was acidified with concentrated HCl to pH=5-6 and was evaporated to dryness to afford a yellow residue. Brine (30 mL) was added to the residue, extracted with CH_2Cl_2 (2 X 20 mL), dried over anhydrous $MgSO_4$, and was evaporated to dryness to obtain a yellow oil. The crude oil was purified by flash column chromatography on silica gel with EtOAc-hexane (1:2) as eluent to give an additional white solid (285 mg, 18%). Crystallization from EtOAc-hexane gave an analytically pure product.

Example 4-A :

Preparation of 1-[(benzyloxy)methyl]-6-[3,5-dimethylphenyl]selenenyl]-5-isopropyluracil (Compound No. **4**)

[0070] To a stirred suspension of 1-[(benzyloxy)methyl]-6-[3,5-dimethylphenyl]selenenyl]-5-isopropyl-2-thiouracil (0.26 g, 0.68 mmol) in aqueous 1N NaOH (6 mL) was added 35% H_2O_2 (0.40 mL, 4.08 mmol). After the mixture was stirred at room temperature for 1 h, the reaction mixture was neutralized with concentrated HCl. The resulting precipitate was filtered and washed well with saturated $NaHCO_3$ solution (3 X 5 mL) and H_2O (3 X 5 mL). The precipitate was thoroughly dried in vacuo over P_2O_5 and crystallized from EtOAc-hexane to give 0.22 g (88%) of the target compound
Yield: 15%;
IR(KBr): 1708, 1645 cm^{-1} ;
^1H NMR($CDCl_3$/TMS): δ 1.08 (d, *J*=6.9 Hz, 6 H, $CH(CH_3)_2$), 2.24 (s, 6 H, 2 CH_3), 3.41 (septet, *J*=6.9 Hz, 1 H, $CH(CH_3)_2$), 4.64 (s, 2 H, CH_2Ph), 5.73 (s, 2 H, NCH_2O), 6.88 (s, 1 H, Ar H), 6.96 (s, 2 H, Ar H), 7.26-7.37 (m, 5 H, Ar H), 8.81 (br s, 1 H, NH)

Example 4-B :

Preparation of 1-[(benzyloxy)methyl]-6-[3,5-dimethylphenyl]selenenyl]-5-isopropyluracil (Compound No. **4**)

[0071] The titled compound was prepared in the same manner as described in Example 3-B by using 1-[(benzyloxy) methyl]-6-chloro-5-isopropyluracil in place of 6-chloro-1-(ethoxymethyl)-5-isopropyluracil.
Yield: 100%;

Comparative Example 1 :

Preparation of 6-[(3,5-dimethylphenyl)selenenyl)-1-(ethoxymethyl)-5-ethyl-2-thiouracil

[0072] The titled compound was prepared in the same manner as described in Example 1 by using bis(3,5-dimethylphenyl) diselenide in place of diphenyl diselenide.
Yield: 74%;
IR (KBr): 1650 cm^{-1} ;
^1H NMR($CDCl_3$/TMS): δ 0.87 (t, *J*=7.4 Hz, 3 H, CH_2CH_3), 1.19 (t, *J*=6.9 Hz, 3 H, OCH_2CH_3), 2.28 (s, 6 H, 2 CH_3), 2.64

(q, J=7.4 Hz, 2 H, CH_2CH_3), 3.68 (q, J=6.9 Hz, 2 H, OCH_2CH_3), 6.20 (br s, 2 H, NCH_2O), 6.92 (s, 1 H, Ar H), 6.98 (s, 2 H, Ar H), 10.03 (br s, 1H, NH)

Comparative Example 2:

Preparation of 1-[(benzyloxy)methyl]-6-[(3,5-dimethylphenyl)selenenyl]-5-ethyl-2-thiouracil

[0073] The titled compound was prepared in the same manner as described in Example 1 by using 1-[(benzyloxy) methyl]-5-ethyl-2-thiouracil and bis(3,5-dimethylphenyl) diselenide in place of 1-(ethoxymethyl)-5-ethyl-2-thiouracil and diphenyl diselenide, respectively.
Yield: 43%;
IR (KBr): 1700 cm^{-1} ;
^1H NMR($CDCl_3$/TMS): δ 0.84 (t, J=7.4 Hz, 3 H, CH_2CH_3), 2.25 (s, 6 H, 2 CH_3), 2.59 (q, J=7.4 Hz, 2 H, CH_2CH_3), 4.73 (s, 2 H, CH_2Ph), 6.27 (br s, 2 H, NCH_2O), 6.90 (s, 1 H, Ar H), 6.93 (s, 2 H, Ar H), 7.25-7.33 (m, 5 H, Ar H), 9.48 (br s, 1 H, NH)

Comparative Example 3 :

Preparation of 6-[3,5-dimethylphenyl]selenenyl]-1-(ethoxymethyl)-5-isopropyl-2-thiouraci l

[0074] The titled compound was prepared in the same manner as described in Example 1 by using 1-(ethoxymethyl)-5-isopropyl-2-thiouracil and bis(3,5-dimethylphenyl) diselenide in place of 1-(ethoxymethyl)-5-ethyl-2-thiouracil and diphenyl diselenide, respectively.
Yield: 83%;
IR (KBr): 1651 cm^{-1} ;
^1H NMR($CDCl_3$/TMS): δ 1.01 (d, J=6.9 Hz, 6 H, $CH(CH_3)_2$), 1.21 (t, J=7.1 Hz, 3 H, OCH_2CH_3), 2.28 (s, 6 H, 2 CH_3), 3.35 (septet, J=6.9 Hz, 1 H, $CH(CH_3)_2$), 3.69 (q, J=7.1 Hz, 2 H, OCH_2CH_3), 6.27 (br s, 2 H, NCH_2O), 6.92 (s, 1 H, Ar H), 7.01 (s, 2 H, Ar H), 9.44 (br s, 1 H, NH)

Comparative Example 4 :

Preparation of 1-[(benzyloxy)methyl]-6-[(3,5-dimethylphenyl)selenenyl]-5-isopropyl-2-thio uracil

[0075] The titled compound was prepared in the same manner as described in Example 1 by using 1-[(benzyloxy) methyl]-5-isopropyl-2-thiouracil and bis(3,5-dimethylphenyl) diselenide in place of 1-(ethoxymethyl)-5-ethyl-2-thiouracil and diphenyl diselenide, respectively.
Yield: 20%;
IR (KBr): 1645 cm^{-1} ;
^1H NMR($CDCl_3$/TMS): δ 0.99 (d, J=6.9 Hz, 6 H, $CH(CH_3)_2$), 2.25 (s, 6 H, 2 CH_3), 3.33 (septet, J=6.9 Hz, 1 H, $CH(CH_3)_2$), 4.73 (s, 2 H, CH_2Ph), 6.37 (br s, 2 H, NCH_2O), 6.90 (s, 1 H, Ar H), 6.97 (s, 2 H, Ar H), 7.25-7.38 (m, 5 H, Ar H), 9.35 (br s, 1 H, NH)

Example 5 :

[0076]

Production of tablet	
6-[(3,5-dimethylphenyl)selenenyl]-1-(ethoxymethyl)-5-isopropyluracil (Compound No. 3)	10 g
Lactose	70 g
Crystalline cellulose	15 g
Magnesium stearate	5 g
Total weight	100 g

[0077] The above-mentioned components were well mixed and tablets were produced by a direct tableting method. Each tablet had a weight of 100 mg and contained 10 mg of 6-[(3,5-dimethylphenyl)selenenyl]-1-(ethoxymethyl)-5-iso-

propyluracil.

Example 6 :

[0078]

Production of powder and encapsulated medicine	
6-[(3,5-dimethylphenyl)selenenyl]-1 -(ethoxymethyl)-5-isopropyluracil (Compound No. 3)	10 g
Corn starch	50 g
Carboxycellulose	40 g
Total weight	100 g

[0079] The above-mentioned components were well mixed to obtain a powder general formulation. Capsule was obtained by encapsulating 100 mg of the thus obtained powder into a hard capsule of No. 5.

Example 7: Inhibitory Activity for HIV-induced Cytopathogenicity

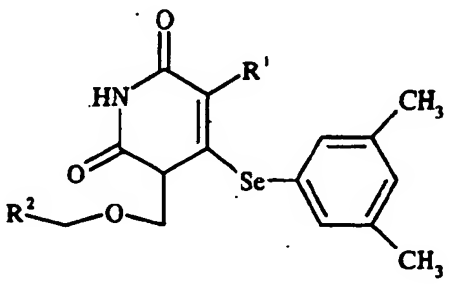
[0080] In RPMI 1640 culture medium supplemented with 10% heat-inactivated fetal bovine serum, 2 mM of L-glutamine, 100 U/mL of penicillin G and 100 μg/mL of streptomycin, MT-4 cells (HTLV-1 transformed T4-cell line) at a concentration of 1 X 10^4 /well in a flat-bottom, microtiter plate were infected with 500 $TCID_{50}$ of HIV-1 (HTLV-III_B strain). Immediately after virus infection, sample serially diluted with culture medium from stock solution prepared in dimethyl sulfoxide was added to each well in quadriplicate. After 6 days incubation at 37°C, the viability of mock and HIV-infected cells was determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method. And also, the cytotoxicity of sample to MT-4 cells not infected with HIV was assessed in parallel with its antiviral activity under the same way as above. These results are presented in Table 2.

Table 2

Compound No.	50% inhibitory concentration of HIV infection (μM)	50% cytotoxic concentration to MT-4 cells (μM)
1	0.0006	28.9
2	0.00008	31.7
3	0.00007	29.2
4	0.000021	30.2
AZT	0.0046	22.7
DDC	0.60	17.6

Claims

1. A pyrimidine acyclonucleoside derivative represented by the following general formula (I):



(I)

wherein
R_1 is ethyl or isopropyl group, and
R_2 is methyl or phenyl group,
or a pharmaceutically acceptable salt thereof.

2. A pyrimidine acyclonucleoside derivative according to claim 1, wherein said general formula (I) is 1-(ethoxymethyl)-5-ethyl-6-[(3,5-dimethylphenyl)-selenenyl]-uracil or a pharmaceutically acceptable salt thereof.

3. A pyrimidine acyclonucleoside derivative according to claim 1, wherein said general formula (I) is 1-(benzyloxymethyl)-5-ethyl-6-[(3,5-dimethylphenyl)-selenenyl]-uracil or a pharmaceutically acceptable salt thereof.

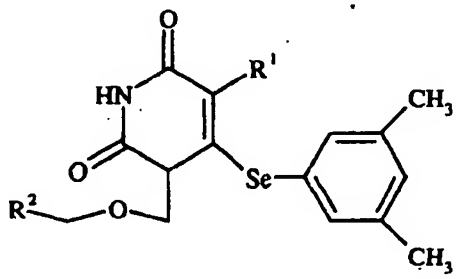
4. A pyrimidine acyclonucleoside derivative according to claim 1, wherein said general formula (I) is 1-(ethoxymethyl)-5-isopropyl-6-[(3,5-dimethylphenyl)-selenenyl]-uracil or a pharmaceutically acceptable salt thereof.

5. A pyrimidine acyclonucleoside derivative according to claim 1, wherein said general formula (I) is 1-(benzyloxymethyl)-5-isopropyl-6-[(3,5-dimethylphenyl)-selenenyl]-uracil or a pharmaceutically acceptable salt thereof.

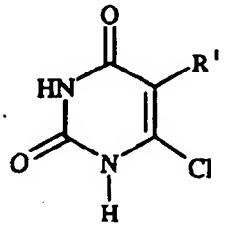
6. An antiviral agent comprising as an active ingredient a pyrimidine acyclonucleoside derivative or a pharmaceutically acceptable salt thereof according to any of claims 1 to 5.

7. A pharmaceutical composition comprising a pyrimidine acyclonucleoside derivative of any of claims 1 to 5 or a pharmaceutically acceptable salt thereof in association with a pharmaceutical vehicle.

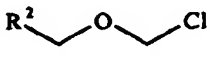
8. A method for preparing a pyrimidine acyclonucleoside derivative represented by the following general formula (I) comprising the steps of reacting an uracil of the general formula (II) with N,O-bis-(trimethylsilyl)-acetamide followed by tetrabutylammonium iodide and a chloromethyl ether of the general formula (III), and reacting a compound of the following general formula (IV) with an aryl selenol in the presence of base, wherein R_1 represents ethyl group or isopropyl group and R_2 represents methyl group or phenyl group.



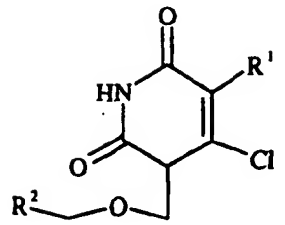
(I)



(II)



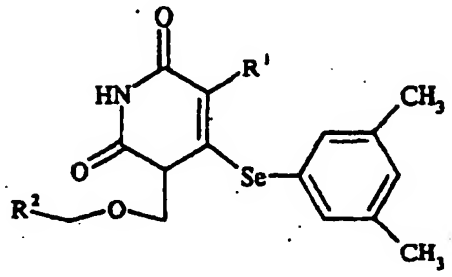
(III)



(IV)

Patentansprüche

1. Pyrimidinacyclonucleosid-Derivat, wiedergegeben durch die folgende allgemeine Formel (I):



(I)

worin,
R_1 eine Ethyl- oder Isopropylgruppe ist und
R_2 eine Methyl- oder Phenylgruppe ist,
oder ein pharmazeutisch verträgliches Salz davon.

2. Pyrimidinacyclonucleosid-Derivat nach Anspruch 1, wobei die allgemeine Formel (I) 1-(Ethoxymethyl)-5-ethyl-6-[(3,5-dimethylphenyl)-selenenyl]-urazil oder ein pharmazeutisch verträgliches Salz davon ist.

3. Pyrimidinacyclonucleosid-Derivat nach Anspruch 1, wobei die allgemeine Formel (I) 1-(Benzyloxymethyl)-5-ethyl-6-[(3,5-dimethylphenyl)-selenenyl]-urazil oder ein pharmazeutische verträgliches Salz davon ist.

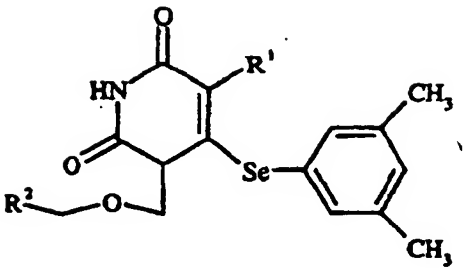
4. Pyrimidinacyclonucleosid-Derivat nach Anspruch 1, wobei die allgemeine Formel (I) 1-(Ethoxymethyl)-5-isopropyl-6-[(3,5-dimethylphenyl)-selenenyl]-urazil oder ein pharmazeutisch verträgliches Salz davon ist.

5. Pyrimidinacyclonucleosid-Derivat nach Anspruch 1, wobei die allgemeine Formel (I) 1-(Benzyloxymethyl)-5-isopropyl-6-[(3,5-dimethylphenyl)-selenenyl]-urazil oder ein pharmazeutische verträgliches Salz davon ist.

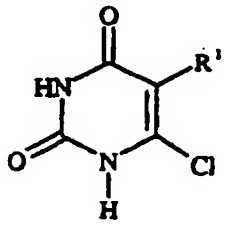
6. Antivirales Mittel, welches als einen aktiven Bestandteil ein Pyrimidinacyclonucleosid-Derivat oder ein pharmazeutisch verträgliches Salz davon nach einem der Ansprüche 1 bis 5 enthält.

7. Pharmazeutische Zusammensetzung, welche ein Pyrimidinacyclonucleosid-Derivat nach einem der Ansprüche 1 bis 5 oder ein pharmazeutisch verträgliches Salz davon zusammen mit einem pharmazeutischen Träger enthält.

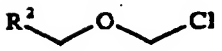
8. Verfahren zur Herstellung eines Pyrimidinacyclonucleosid-Derivats, wiedergegeben durch die folgende allgemeine Formel (I), mit den Stufen, in denen man ein Urazil der allgemeinen Formel (II) mit N,O-Bis-(trimethylsilyl)-acetamide, gefolgt von Tetrabutylammoniumiodid und einem Chlormethylether der allgemeinen Formel (III) umsetzt und eine Verbindung der folgenden allgemeinen Formel (IV) mit einem Arylselenol in Gegenwart einer Base umsetzt, wobei R_1 eine Ethylgruppe oder eine Isopropylgruppe und R_2 eine Methylgruppe oder eine Phenylgruppe darstellt.



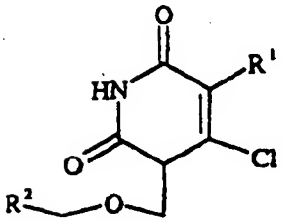
(I)



(II)



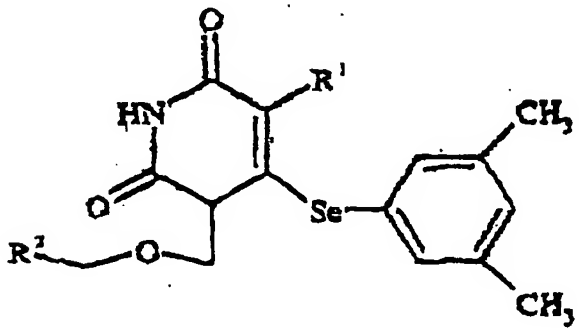
(III)



(IV)

Revendications

1. Dérivé de la pyrimidine acyclonucléoside ayant la formule générale suivante (I) :



(I)

où
R_1 est un groupe éthyle ou isopropyle, et
R_2 est un groupe méthyle ou phényle,
ou un sel de celle-ci acceptable du point de pharmaceutique.

2. Dérivé de la pyrimidine acyclonucléoside selon la revendication 1, dans lequel ladite formule générale (I) est le 1-(éthoxyméthyl)-5-éthyl-6-[(3,5-diméthylphényl)-sélényl]-uracile ou un sel de celle-ci acceptable du point de vue pharmaceutique.

3. Dérivé de la pyrimidine acyclonucléoside selon la revendication 1, dans lequel ladite formule générale (1) est le 1-(benzyloxyméthyl)-5-éthyl-6-[(3,5-diméthylphényl)-sélényl]-uracile ou un sel de celle-ci acceptable du point de vue pharmaceutique.

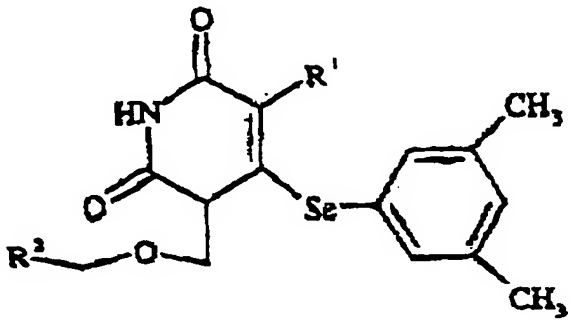
4. Dérivé de la pyrimidine acyclonucléoside selon la revendication 1, dans lequel ladite formule générale (I) est le 1-(éthoxyméthyl)-5-isopropyl-6-[(3,5-diméthylphényl)-sélényl]-uracile ou un sel de celle-ci acceptable du point de vue pharmaceutique.

5. Dérivé de la pyrimidine acyclonucléoside selon la revendication 1, dans lequel ladite formule générale (I) est le 1-(benzyloxyméthyl)-5-isopropyl-6-[(3,5-diméthylphényl)-sélényl]-uracile ou un sel de celle-ci acceptable du point de vue pharmaceutique.

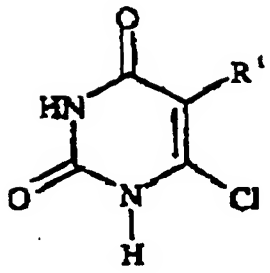
6. Agent antiviral comprenant comme principe actif un dérivé de la pyrimidine acyclonucléoside ou un sel de celle-ci acceptable du point de vue pharmaceutique selon l'une quelconque des revendications 1 à 5.

7. Composition pharmaceutique comprenant un dérivé de la pyrimidine acyclonucléoside selon l'une quelconque des revendications 1 à 5 ou un sel de celle-ci acceptable du point de vue pharmaceutique en association avec un porteur pharmaceutique.

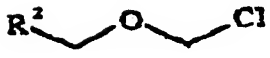
8. Procédé pour préparer un dérivé de la pyrimidine acyclonucléoside ayant la formule générale suivant (I) comprenant les étapes consistant à faire réagir un uracile ayant la formule générale (II) avec un N_2O-bis-(triméthylsilyl)-acétamide suivi d'un iodure de tétrabutylammonium et d'un éther de chlorométhyle ayant la formule générale (III), et à faire réagir un composé ayant la formule générale suivante (IV) avec un sélénol d'aryle en présence d'une base, où R_1 est un groupe éthyle ou un groupe isopropyle et R_2 est un groupe méthyle ou un groupe phényle.



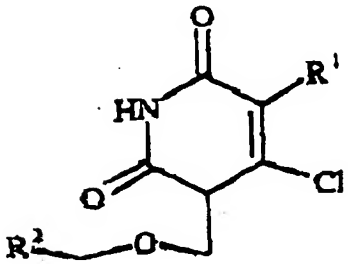
(I)



(II)



(III)



(IV)